HYPERTENSIVE DISEASE

Diagnosis and Treatment



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BY

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HYPERTENSIVE DISEASE
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Preface

Although the cause of essential hypertension is still a mystery, it is now possible to bring about effective reduction in the blood pressure level by appropriate treatment. Survival rates following sympathectomy, as well as daily experiences in the practical management of the disease, demonstrate that in the main blood pressure reduction is beneficial rather than harmful as once was thought. Three factors are primary in determining the survival of the patient with hypertension: (1) the height of the blood pressure, (2) the duration of its elevation, and (3) the vulnerability of the arterial system to the morbid process. Successful treatment has a dimension of time as well as magnitude

The effective use of procedures for bringing the blood pressure temporarily under control is widespread in the United States today, but methods to maintain blood pressure reduction and to assess vascular vulnerability in this disease are little understood. This book is intended to bring to medical practitioners knowledge of those procedures that have been developed in special clinics for the treatment of hypertension. It is based largely on the author's ten years of experience as Director of the Hypertension Unit at the University of Michigan Hospital. All phases of patient management are included whether the treatment is given at home, at the office, or in the hospital.

The first two sections of the book describe criteria for the recognition of secondary forms of hypertension and give recommendations for the treatment of those types susceptible to cure The three sections that follow are devoted to the diagnosis and treatment of primary hypertension and its complications and include a thorough discussion of the principles underlying treatment. Specific treatment regimens designed to reduce the blood pressure are considered, giving the pharmacodynamics, advantages, and disadvantages of particular therapeutic agents, as well as

discussing operative procedures and other methods of treatment. The twelve Appendixes contain precise details and techniques for tests and for treatment, including the handling of hypertensive emergencies. This section was designed to be of maximum aid to the physician for quick reference. Specific instructions are given for the choice of patient, drug dosage, contraindications and side effects, and total patient management. Throughout the text of the book case histories have been incorporated to emphasize the clinical viewpoint.

The management of patients with hypertension has entered a phase not unlike that which confronted the physician when insulin first became available for diabetes. Success in treatment requires a high degree of understanding and co-operation on the part of patient and physician. The practical difficulties in the way of long-term management should be looked upon as a challenge to devise more convenient and logical techniques for using available drugs. It is hoped that this book, with its clinical emphasis, will be of assistance to the physician in the effective treatment of his patients with hypertensive disease.

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SECTION I

SECONDARY HYPERTENSION SUSCEPTIBLE TO CURE



CHAPTER 1



"Curable" Renal Hypertension

Immediately following Doctor Goldblatt's epochal report of the production of experimental renal hypertension in the dog by partially clamping one or both renal arteries (Goldblatt, 1934), physicians began to identify the apparent clinical counterpart, and in cases of unilateral renal disease, nephrectomy was advised. Disappointment over the frequent failure of this procedure to lower the blood pressure led to a period of skepticism, but two recent reviews leave little doubt that in the properly selected case a permanent cure can be effected (Smith, 1956; Thompson, 1957). The diagnosis of this condition has been made with greater frequency since it has been recognized that aortography might reveal renal vascular lesions not suspected from intravenous pyelograms (Poutasse, 1956a).

In the dog, clamping one renal artery leads to transient hypertension that can be made permanent only by contralateral renal artery constriction or nephrectomy. In the rat, obstructing the blood supply to one kidney often leads to sustained hypertension. Removal of this kidney restores normotension as long as the contralateral kidney is free of hypertensive vascular disease (Byrom, 1949). *In man as in the rat, partial obstruction of one* renal artery may give rise to sustained hypertension, and removal of the kidney or of the arterial obstruction has relieved hypertension that has been present for as long as 6 years (Poutasse, 1956a; Margolin, 1957). On the other hand, hypertension from a unilateral renal lesion may produce sufficient

vascular damage in the contralateral kidney to perpetuate the hypertension after removal of the initially offending kidney. Even in the presence of considerable impairment of contralateral renal function, however, reduction of the blood pressure by removing the abnormally perfused kidney may, over a period of many months, result in gradual improvement of the contralateral kidney with restoration of normal renal function (Imber, 1955).

In man, a great variety of curable renal lesions has been described, but in general they may be placed in four categories:

1. Obstructive lesions of the renal vessels
2. Old, healed pyelonephritis
3. Obstruction of the ureters on one or both sides
4. Lesions causing shrinkage or interference with the renal capsule (Wilms tumor, renal hematoma, irradiation of the kidney, etc.)

CLINICAL FEATURES OF HYPERTENSION OF CURABLE RENAL ORIGIN

The clinical aspects of *obstructive arterial lesions* are well reviewed by Margolin, Merrill, and Harrison (1957). Such a lesion may be suspected when there is a record of the sudden onset of extreme polyuria or dysuria, when albuminuria is prominent, or when one kidney is smaller than the other. When a sudden severe rise in the blood pressure occurs in a patient who was known to be normotensive in the previous two or three years, and especially when this patient is without a family history of hypertension, a curable renal vascular lesion is to be suspected. Perera (1952) maintains that since essential hypertension always develops before the later years of life, renal hypertension is to be suspected when an elderly person with a previous history of normal blood pressure experiences the sudden onset of marked hypertension. Finally, total vascular obstruction with consequent renal infarction may lead to elevation of the blood pressure, as in the case reported by Howard (1954) in which the occlusion caused severe back pain and was followed by hypertension.

When there is a history of *pyelonephritis* or other urinary tract infection, one should consider the possibility of a curable renal lesion. Although the disease is often bilateral, intravenous and

retrograde pyelograms may be necessary to establish this fact. Severe hypertension caused by a unilateral healed pyelonephritis is frequently unaccompanied by a characteristic history and is detected only by pyelographic studies.

Obstructive lesions of the ureters are an exceptional cause of hypertension. Total complete obstruction of one or both ureters rapidly results in pressure atrophy of the kidney without elevation of the blood pressure. Partial obstruction, if it develops gradually, may cause hypertension and be found without oliguria or anuria, either because the obstruction is unilateral or because a high intrapelvic pressure may force urine past a bilateral obstruction. Such a syndrome has been seen in a few cases in our clinic, once as a result of ureteral obstruction following extensive x-ray therapy to the pelvic region, once following carcinomatous infiltration of the ureter, and once in a young man with a congenital urethral valve. A most interesting case in which this mechanism may have been involved has been described by Dr. Reed Nesbit (1958). The patient was a young girl with vesico-ureteral backflow evident on cystograms. The child was able to go for as long as 24 hours without voiding because of the large capacity of the bladder, ureter, and kidney pelvis. When she was trained to void regularly at 2-hour intervals, the ureteral reflux disappeared and the hypertension subsided. Although the relationship between hypertension and renal disease in this case is more doubtful than in the others cited, these scattered experiences indicate the importance of investigating the renal excretory system in obscure cases of severe and unusual hypertension.

In the varied forms of hypertension secondary to unilateral renal disease, there are no unusual *physical findings*, except that the blood pressure elevation may vary from mild to severe, is usually rapidly progressive, and commonly is associated with marked retinopathy. Smithwick (1957) has reported that a reduction in blood pressure on assuming the erect posture is common in renal hypertension.

Routine *laboratory findings* are not diagnostic, although a tendency to leukocytosis has been described (Margolin, 1957). The urine may be entirely normal or, if polyuria and nocturia are the complaints, the urine concentrating ability may be impaired.

Albuminuria and signs of infection may or may not occur. The renal function varies from near normal to the range of azotemia.

SPECIAL DIAGNOSTIC PROCEDURES

Intravenous pyelograms are required in severe hypertension to exclude a unilateral renal origin (Table 1). They should be performed in all cases of recent onset in which the disease is definitely established. When the hypertension is of long duration, the question is often raised whether it is worthwhile to perform pyelograms since chronic renal hypertension rarely responds to nephrectomy. However, previously mild hypertension may have been aggravated by the more recent development of a curable renal vascular lesion. Furthermore, since some cases of more than 5 years' duration have been reported to be cured by nephrectomy (Margolin, 1957), it is not impossible that pyelography may lead to the discovery of a curable renal lesion even in cases of prolonged hypertension.

When hypertension is accompanied by renal excretory insufficiency, pyelography is useless since the kidneys will not visualize. If a unilateral renal lesion had initiated the hypertension in such a case, it may be argued that the contralateral kidney has become so diseased as to render the condition irreversible even following removal of the originally involved kidney. Occasionally, however, special studies are advisable in hypertension accompanied by azotemia. When there is a possibility that the unilateral renal lesion was of very recent origin as in the case described by Imber (1955), or when bilateral obstructive uropathy is a possibility, certain renal investigations may be justified. Abdominal x-rays may indicate the size of the kidneys or the presence of ureteral calculi or other cause of obstruction. Aortograms are generally contraindicated by the danger of aggravating the renal insufficiency. Retrograde investigations are dangerous and should be avoided unless there is real likelihood of making a diagnosis that can lead to successful treatment.

Intravenous pyelograms may reveal distortion or displacement of one kidney, or provide evidence of decreased size or of absence of visualization on one side. The x-ray findings most likely to be significant, in order of descending importance, are: (1) a

TABLE 1. "CURABLE" UNILATERAL RENAL HYPERTENSION—DIAGNOSTIC FEATURES

Clinical features	*Pathological aspects*	*I V. Pyelograms*	*Aortograms indicated*
Recent onset of severe hypertension	Renal artery obstruction	Not always diagnostic	Yes
Hypertension with papilledema in elderly patients	Arteriosclerotic renal obstruction	Not always diagnostic	Yes
Hypertension after back pain or hematuria	Renal infarction	Not always diagnostic	Yes
All children with severe hypertension	Varied	Not always diagnostic	Yes
Chronic severe hypertension	Old chronic unilateral pyelonephritis	Nonvisualization or very small kidney	No, retrograde pyelograms first choice
	or		
	Renal artery obstruction, or infarction	Kidney size somewhat reduced or poorly visualized	Yes
	or		
	Hydronephrosis from aberrant renal artery or calculous obstruction	Hydronephrosis or ureteral abnormality	No, retrograde pyelograms

In azotemia or hypertension exceeding 5 years, cure is improbable. (See text for details.)

renal shadow less than 80 per cent of the size of its counterpart, (2) nonvisualization on one side, (3) delayed or distinctly reduced excretion of contrast medium on one side, and (4) evidence suggesting unilateral hydronephrosis or pyelonephritis.

In certain situations pyelograms will appear to be normal despite the presence of a partial unilateral renal arterial obstruction causing hypertension. This follows from the fact that a pyelogram shows only very grossly the excreted radiopaque medium, and the density of the shadow is further dependent on urine flow, ureteral peristalsis, overlying intestinal shadows, and other factors. These may influence the comparative renal density far more than a partial reduction in the inflow of blood. Since the kidney excretes in a single circulation all contrast medium that perfuses it, it is evident that a dense excretory shadow can rapidly appear even when blood flow to one kidney is deficient.

If further study seems indicated, *retrograde pyelography* may be considered. When one kidney is not visualized on intravenous pyelograms, agenesis must be excluded. Failure to find a ureteral orifice on retrograde cystoscopic examination is most helpful in this situation. However, this procedure should be withheld unless the hypertension is serious, in which case appropriate antibiotic premedication should be carried out to prevent possible infection of the single kidney. If the ureters can be entered, retrograde pyelograms are the best means for demonstrating obstructive uropathy or an old pyelonephritis. Vascular lesions, however, are less likely to be demonstrated by this procedure. When retrograde examination is performed, the renal function of each kidney should be determined separately and with the greatest possible accuracy. Unfortunately, random variations in urine flow and leakage around the catheter often make it difficult to be certain of comparative renal function on the two sides. However, the appearance time of an indicator such as phenolsulfonphthalein or indigo carmine, when urine flow has been accelerated by a high fluid intake, may indicate comparative renal functions. Similarly, the sodium and creatinine concentrations of ureteral urine are also independent of leakage around the catheters. This examination has recently been advocated for identifying a unilateral arterial obstruction on the basis of the fact that in a kidney with reduced renal arterial pressure, sodium reabsorption is increased (Howard, 1954). However, this pro-

cedure appears less reliable than aortography in identifying vascular obstructive lesions (Dustan, 1957).

Aortography is generally more useful than retrograde pyelography as a diagnostic technique. The indications for this examination are outlined in Table 1. The procedure carries some risk, however, and should not be performed unless the hypertension is severe enough to justify nephrectomy should a lesion be found. This criterion applies even more forcibly when renal failure is actual or impending. The procedure will not ordinarily distinguish between renal agenesis and an old atrophic pyelonephritis. For this purpose retrograde studies are preferable. Aortography is useful in studying those patients with severe *hypertension of recent onset who have apparently normal in-* [illegible] were found.

Renograms, in which renal uptake of I^{131} *labeled Diodrast is* compared by external counting over both kidneys, has also proved useful in identifying cases of renal ischemia (Winter, 1957).

Needle biopsy of the kidney has been of great investigative and occasional therapeutic value in locating a pyelonephritic lesion that is causing hypertension but is not reflected in urinary findings (Kark, 1955). Such lesions are usually bilateral. The area may be missed by the needle; consequently, a negative biopsy report does not exclude pyelonephritis. The procedure is not likely to influence the physician's treatment frequently enough to justify its routine use in identifying a renal lesion possibly causing hypertension.

TREATMENT OF UNILATERAL RENAL LESIONS

Treatment for such renal lesions as have been described above usually consists in nephrectomy or replacing the obstructed renal artery with a vascular graft. The former is preferred when the kidney reveals very poor function; the latter is useful when good renal function is present, the surgeon is skillful, and the obstruction is not too close to the aorta. The use of vascular transplants as reported by Poutasse (1956) is particularly valuable, since

the procedure preserves normally functioning renal tissue which may counteract the pressor effects of the secondarily damaged opposite kidney. In experimental renal hypertension, unclamping the renal artery is more likely to cure the hypertension than is unilateral nephrectomy (Byrom, 1949).

The problem of whether to advise nephrectomy in long-standing hypertension or in hypertension with azotemia frequently arises. In the former situation, no arbitrary rule can apply to all cases but occasionally improvement in the blood pressure may follow the operation. Removal of a kidney capable of good excretory function is unwise in this situation. In renal insufficiency, Imber (1955) has reported one successful experience following nephrectomy. In one case at the University of Michigan Hospital where nephrectomy was performed in a cardiac hypertensive patient with moderate azotemia, the result was most impressive. Despite these occasional examples, nephrectomy for severe hypertension would seem hazardous in the presence of azotemia. The only justification lies in the fact that surgical cure, when attainable, far exceeds the value of treatment with any drug now available.

It may well be questioned whether it is ever justifiable to remove kidney tissue that is contributing to renal excretory function, in the hope of alleviating hypertensive disease. In general, since severe hypertension alone will cause further renal deterioration, any method to lower the blood pressure is justified provided sufficient functional tissue remains for the patient's survival, and provided, of course, that the lesion to be removed is the most probable cause of the hypertensive disease.

Since the contralateral kidney may have suffered vascular damage from the hypertension and may in itself perpetuate the disease, "cure" by nephrectomy can be expected in less than 50 per cent of the cases even when these are carefully selected. The patient should be warned of this possibility so that he may not expect too much. Nevertheless, nephrectomy or excision of a renal arterial obstruction with insertion of a vascular graft remains the most satisfactory curative procedure in serious hypertensive disease.

The following experience illustrates some of the considerations mentioned previously.

Case History

A 48-year-old man was admitted to the hospital because of occipital headaches and occasional nausea and vomiting for the preceding 10 months. He had been told at the onset of these latter symptoms that his blood pressure was elevated. The only known previous blood pressure reading, 16 years before, had been normal. There was no family history of hypertension. The blood pressure on admission was 240/140 mm. Hg. Retinal examination showed Grade III vascular constriction without hemorrhage, exudate, or papilledema. No other relevant abnormalities were found.

Laboratory studies were as follows: Urine: trace of albumen, numerous hyaline casts, and a specific gravity of 1.022, phenolsulfonphthalein excretion in 15 minutes: 30 per cent (normal); complete blood count: normal; creatinine clearance: 167 liters per 24 hours (high normal); electrocardiogram: within normal limits; intravenous pyelograms: the left kidney shadow was slightly smaller than the right, Regitine test: negative.

The patient was treated successfully with mecamylamine: standing blood pressure readings fell to 100/50 to 150/100 mm. Hg with 12.5 mg. of the drug twice daily. Because of the apparently recent onset of symptoms, the severity of hypertension, and the lack of evidence of long-standing disease, aortograms were obtained. These showed marked narrowing of the left renal artery at its origin from the aorta and subsequent poststenotic dilation. The vascular pattern of both kidneys appeared normal although the density of the renal shadow on the left was reduced, and the size of the left kidney was smaller than the right.

Mecamylamine was discontinued and nephrectomy was performed, the area of stenosis being too close to the aorta to permit a successful vascular transplant. The patient's blood pressure, which was 200/130 mm. Hg during the operation, fell to 140/100 mm. at the end of the procedure.

Since his discharge, his blood pressure has been reported to be normal on weekly visits to his personal physician. At a 6-month postoperative visit to the Hypertension Clinic, he stated that he had had no further headaches. His blood pressure was 166/100 mm. Hg (casual) and 134/84 mm. (resting). The re-

moved kidney weighed 155 Gm. and was grossly and microscopically normal in appearance.

COMMENT. None of the more obvious clinical features of unilateral renal disease suggested the diagnosis. Pyelograms were normal. Aortograms were nevertheless recommended because of the apparently recent onset of severe hypertension. This was surmised from the history of the abrupt onset of headaches and severe blood pressure elevation in a man without any renal, retinal, or electrocardiographic signs of prolonged vascular disease. Our recommendation was further supported by the complete lack of a family history of hypertension. The nephrectomy in this case reduced the blood pressure within a few minutes. In other cases reductions have been less immediate but usually have occurred within a few days after surgery. It is interesting to note that this patient with obvious "humoral" hypertension exhibited a normal responsiveness to ganglionic blocking agents.

It is possible that cases such as this one are frequently overlooked, particularly when no obvious indication for aortography is apparent. The most suggestive sign was the apparent recent onset of hypertension in a subject without a family history of the disease. Because hypertension in a male patient carries a more serious prognosis, and because these renal vascular anomalies appear more frequently in men (Margolin, 1957), perhaps aortographic examinations are especially advisable in this sex.

SUMMARY

The possibility of a curable renal lesion should be considered in the investigation of all cases of serious hypertension, since such a lesion may occur without characteristic symptoms or laboratory findings. In hypertension that is associated with azotemia or exceeds 5 years in duration, cure by nephrectomy is unlikely even if a primary renal lesion is discovered. When the disease is of recent onset and of considerable severity, or when malignant hypertension arises in childhood or in patients over 50, a renal origin is very likely and aortographic studies should be carried out. In some instances, particularly when renal arterial obstruction is suspected, only aortograms will show the defect.



CHAPTER 2



"Curable" Hypertension: Pheochromocytoma

SYMPTOMS

In the history of the patient with normal blood pressure or with hypertension, the commonest symptoms characteristic of pheochromocytoma are recurrent attacks of severe *headache* that may be occipital or generalized, *palpitation* recognized as a more forceful heart beat by an introspective patient, a sudden inexplicable "internal *nervousness*" without relation to external events, and *tremor, pallor,* and *sweating.* The association of these attacks with *abdominal pain,* nausea, or vomiting is particularly significant. Additional symptoms related to hypertensive vascular disease may also occur, notably transient cerebrovascular disorders and paroxysmal left ventricular failure. Unfortunately, similar complaints appear in a variety of other conditions and must be eliminated by a carefully discriminating history.

DIFFERENTIAL DIAGNOSIS

Anxiety states may, of course, occur without overt connection with the environmental situation of the moment. Symptoms of hyperventilation, such as symmetrical numbness of the fingers and paresthesias about the mouth, are common in this condition and absent in pheochromocytoma. Sudden *cardiac arrhythmias* are sometimes difficult to distinguish from the symptoms of

adrenal medullary tumors, and to make the distinction more confusing, episodes of ventricular premature beats or ventricular tachycardia have been described in association with adrenal tumors. *Functional hypoglycemia* may exhibit many features characteristic of a pheochromocytoma, since low blood sugar is a known stimulus for the release of epinephrine. In this condition episodes occur before luncheon and before dinner. Ingestion of food results in prompt relief, no attacks occur within one to two hours after meals, and the blood pressure is usually not greatly elevated during such an episode. The vasomotor features of the *menopausal syndrome* are similar to some symptoms of pheochromocytoma. The differential diagnosis is not made easier by the fact that the latter condition is often found for the first time in women aged 40 to 50. *Thyrotoxicosis* may also resemble an adrenal medullary tumor and requires exclusion by iodine uptake studies, since tachycardia, hypermetabolism, and glycosuria are common to both conditions.

PHYSICAL FINDINGS

Marked lability of the blood pressure and persistent tachycardia may suggest the diagnosis. The presence of the *café au lait* spots or of the neurofibromata of von Recklinghausen's disease in a hypertensive patient should stimulate the examiner most particularly to exclude pheochromocytoma, since there is a frequent association between these two diseases—presumably based on primordial embryonic tissue that is of similar origin for the neurofibroma and the pheochromocytoma. Certain other physical signs may provide the initial clue to the diagnosis of pheochromocytoma: a slightly elevated temperature, unexplained postural hypotension, sudden elevation of blood pressure without apparent cause, and in rare cases a palpable abdominal mass or a displaced kidney. Finally, the retinal, cardiac, and neurological findings of hypertensive vascular disease may be found.

ROUTINE LABORATORY TESTS

Glycosuria and *hyperglycemia* may occur in this condition. The apparent coexistence of hypertension and diabetes should

always lead *to consideration of a possible pheochromocytoma.* In practice, most such patients will be found to be victims of diabetic nephropathy, as indicated by the long duration of diabetes, the typical retinal artery lesions, and albuminuria, three features not seen in mild hypertension resulting from pheochromocytoma. An increased *basal metabolic rate* in a hypertensive patient who is not obviously thyrotoxic should suggest the possibility of pheochromocytoma. However, hypertension itself is responsible for a slight elevation of the metabolic rate. The *intravenous pyelogram* may provide a diagnostic lead. Downward displacement of the kidney shadow, particularly on the left side, may suggest the presence of a suprarenal mass such as pheochromocytoma.

PHARMACOLOGIC TESTS

When the blood pressure is below 200 mm Hg systolic at the time of testing, the procedure of choice is the *histamine test* in which .025 mg. of the base is given intravenously (see Appendix 1, p 249). Details of the test procedure should be followed closely. Every effort must be made to prevent anxiety induced by the side effects of the drug from raising the patient's blood pressure. Careful explanation of the reason for the test and the expected nature and duration of side effects is required in advance. The drug should not be injected until the blood pressure has become stabilized, and probably no test should be considered satisfactory unless a transient depression of blood pressure follows the injection. Such a response is so common that its absence suggests that the histamine has inadvertently been administered outside the vein

The results of this testing may be negative, in that the blood pressure does not exceed the preinjection base line, or it may be unequivocally positive, with blood pressure elevations of great magnitude that always occur within a few minutes after the initial depressor phase. Sometimes, especially in nervous patients with very labile hypertension, there is a slight rise in blood pressure over the base line. This may be caused by anxiety, often as a result of the severe headache histamine sometimes causes. Repetition of the test, after careful reassurance and perhaps with

the use of smaller doses, will frequently demonstrate that the original response was a false positive result. Roth and Kvale (1945) in their original description of the test indicated that a mild rise in blood pressure, not exceeding that produced by immersing the hands for one minute in ice water, might normally occur, but in our clinic any rise above the control levels after histamine is exceptional if the patient is carefully prepared for the test procedure. While a negative test is fairly reliable in excluding pheochromocytoma, any equivocal or positive reaction requires further confirmation.

One may proceed immediately to either or both of the following procedures. (1) *Administration of phentolamine* (Regitine). If there is a modest elevation of blood pressure at the time of testing, the injection of Regitine should result in marked hypotension if circulating epinephrine is responsible for the hypertension (see below). (2) *Injection of tetraethylammonium chloride* (Etamon). *This test has a less satisfactory record* of reliability but if it also evokes a pressor response, the diagnosis is beyond doubt (see Appendix 1, p. 250). In evaluation of a positive histamine test, a procedure involving blood pressure reduction is obviously safer than repetition of an evocative test such as histamine, particularly since the patient, having experienced one positive reaction to histamine, will probably be somewhat anxious concerning its repetition. However, if the blood pressure is not greatly elevated, the depressor response to the Regitine test may not be great enough to be of diagnostic value. In this case, repetition of the histamine test or assay of the urine for catechol amines is advised before subjecting the patient to an exploratory laparotomy. The precautions necessary in repeating the histamine test, or in giving it for the first time to a person likely to have a pheochromocytoma, are as follows:

1. Always have Regitine at hand to counteract any possible pressor response.
2. Start with small doses of histamine and increase them gradually (.005 mg. intravenously is a good starting dose).
3. Leave the needle in the vein throughout the procedure and keep it open so that appropriate antidotes can be administered if necessary.

When the blood pressure exceeds 200 mm. Hg systolic, one relies on the screening test with Regitine (Gifford, 1952)

and the confirmatory test with benzodioxane (Goldenberg, 1947) (see Appendix 1, p. 252). It is necessary to follow every detail of these tests with care if the results are to be interpreted correctly.

Unlike the evocative test just described, a positive *response to phentolamine* depends on quantitative rather than qualitative differences. The drug has multiple effects, including competition with epinephrine and norepinephrine for receptor sites on the arteriolar smooth muscle, inhibition of sympathetic vasoconstrictor tone, and a weak direct dilating action on blood vessels. Therefore, it is not surprising that Regitine lowers the blood pressure markedly in most hypertensive patients, but only that it does not do so more frequently. Since all actions of the drug lead toward the same depressor effect, it is hard to distinguish between a positive and a negative test. The differentiation is arbitrarily placed at a reduction of 35 mm. Hg in the systolic and 25 mm. in the diastolic blood pressure. One must rely here on statistical probability, much as with a presumptive Kahn test for syphilis, and expect positive reactions to occur in hypertension as well as in cases of pheochromocytoma. As many as 10 per cent of patients with markedly elevated blood pressure may show a nonspecific false positive reaction Nevertheless, patients who display a barely positive response to the Regitine test should be examined carefully. False positive tests are said to be caused by azotemia or by the coincident use of sedatives, tranquilizers, and antihypertensive drugs (Kvale, 1956). The first step is to repeat the Regitine test, carefully observing the details of the test procedure. Should sedative or hypotensive drugs be used by the patient, these must be omitted prior to repetition of the test. In the case of reserpine, which requires a long time for elimination, the drug should be discontinued for several weeks before repeating the Regitine test. To avoid intermissions in treatment, it is always well to test a hypertensive patient for pheochromocytoma before embarking on a therapeutic program. In patients already under treatment, there can be no objection to performing the screening test immediately and withdrawing the drug only in those individuals who react positively to Regitine. There seems to be no evidence that false negative tests may occur as the result of testing a patient who is under treatment with sedative or tranquilizing drugs.

When the Regitine test has been repeatedly positive or the issue remains in doubt because of one positive and one negative test, the *injection of benzodioxane* (Benodaine) serves as a confirmatory procedure (see Appendix I, p. 252). The pharmacologic action of this drug includes a central excitatory component that increases peripheral sympathetic vasoconstrictor discharge. In addition, it has a weak sympatholytic and adrenolytic action. Consequently, in hypertensive patients without pheochromocytoma there may be a substantial elevation of blood pressure following injection of benzodioxane, while in cases of pheochromocytoma the weak adrenolytic action may result in more frequent false negative reactions. For this reason, the test is less useful for screening purposes. As with Regitine, false positive reactions may occur in azotemia and after sedative drugs.

Three further steps may be taken in excluding pheochromocytoma from the diagnosis, in the patient with greatly elevated blood pressure. First, one may determine the degree of response to Regitine. A dose of 2 5 mg. is given intravenously in the same time required for 5.0 mg. If the response is positive by the criteria used for the standard dose, the likelihood of a nonspecific false positive reaction is reduced. This procedure has proved valid in one case seen in the Hypertension Clinic, but is otherwise without confirmation. A second possible step consists in a careful trial of the histamine evocative test Despite the potential risk of a hypertensive crisis if a pheochromocytoma is present, it is possible to perform the test safely if the following criteria are met: (1) the patient's systolic blood pressure after prolonged resting does not exceed 200 mm. Hg, (2) a small dose (.005 mg.) is used initially, and (3) Regitine is available for immediate intravenous administration. A further step consists in determining the twenty-four hour urinary catechol amine excretion. This will be discussed in a later section.

INDICATIONS AND CONTRAINDICATIONS FOR PHARMACOLOGIC TESTING

It is doubtful how much expenditure of time and energy in testing for pheochromocytoma is justified considering the infrequency with which the diagnosis is made. However, if one such

case is identified and cured by surgery, all the preceding negative tests seem well worthwhile. Consequently, the possibility of this diagnosis should be entertained in every patient with severe hypertension, or with mild hypertension in whom the symptoms may be suggestive. If in a busy office practice these procedures cannot be performed routinely, there is little excuse not to do them in those cases in which the index of suspicion is particularly high (Table 2).

Occasionally these test procedures should not be performed, either because of the almost automatic exclusion of the condition or because of the risks involved in the test. *Obvious anxiety states* with hypertension can usually be identified by the patient's history. In such cases, however, the tests are frequently performed for the complete information of the referring physician. There is probably no objection to such testing provided the patients are appropriately reassured and provided baseline observations are performed carefully enough that a chance rise in blood pressure owing to the anxiety of the patient over the procedure is not considered to be a positive test. Since surgical exploration on the basis of a false positive test would be a grave error, the results of the procedure must be interpreted with discrimination in anxiety states.

Cases of hypertension associated with pheochromocytoma rarely exhibit *azotemia*. In this condition pharmacologic tests depending on depressor effects are often falsely positive Moreover, such tests in uremic subjects have actually led to prolonged circulatory collapse and death (Soffer, 1952). Therefore, they may be omitted in patients with renal insufficiency.

Typical angina pectoris, as contrasted with various syndromes associated with acute elevations of the blood pressure and accompanied by substernal pressure, dyspnea, and inability to get the breath, is also very rarely associated with pheochromocytoma. This again is fortunate, since vasoactive drugs may be dangerous in patients with angina pectoris. Histamine is particularly contraindicated. Regitine may be given with relative safety, but some patients who have received the drug have complained of tachycardia and substernal pain suggesting mild transient coronary insufficiency.

In *congestive heart failure* and in *severe asthma* histamine

TABLE 2. PHEOCHROMOCYTOMA: REVIEW AND SUMMARY

What patients to test	*What test to use*	*Similar syndromes*	*Differential features*
1. Most hypertensive patients	Preliminary screening tests. 1. Histamine 2. Regitine	1. Functional hypoglycemia 2. Anxiety state 3. Hyperthyroidism 4. Menopause 5. Cardiac arrhythmias	1. Food relationship; glucose tolerance test 2. Bilateral paresthesias 3. I^{131} uptake; serum cholesterol 4. Characteristic flushes 5. Normal blood pressure during attack
2. Normotensive persons with characteristic symptoms	Confirmatory tests 1. tetraethylammonium 2. benzodioxane		
3. Especially patients with labile blood pressure and postural hypotension, glycosuria, displaced kidneys, recurrent premature beats	Final test: Urinary catechol amines		

testing also should be avoided. When necessary in such cases pheochromocytoma is best excluded by examination of a 24-hour urine specimen for catechol amines.

CHEMICAL TESTS FOR PHEOCHROMOCYTOMA

Analysis of urine specimens for catechol amines is a difficult procedure usually performed only by specially equipped laboratories and for this reason the test is not employed routinely. Its use is advisable, however, in certain instances:

1. To provide confirmatory evidence of pheochromocytoma in cases in which one or more of the pharmacologic tests have shown a positive response and in which adrenal exploration is under consideration.
2. To examine those patients whose clinical status contraindicates pharmacologic testing (e.g., angina pectoris, severe asthma, or heart failure).
3. As a valuable aid in confirming the nature of a presumptive attack that is or is not witnessed by the physician.
4. To detect whether complete removal of a pheochromocytoma has been accomplished by surgery, especially in the occasional instance in which hypertension persists after identification and excision of the tumor.

The technique of Von Euler and Floding (1955) seems the *best among relatively simple methods. It involves oxidation of* epinephrine to the fluorescent product, adrenochrome, using potassium ferricyanide at pH 6.5 as the oxidizing agent. With this method, 75 to 95 per cent recovery of added epinephrine has been achieved in our laboratory. Oxidation of both catechol amines at this pH is more or less complete, but the result is usually expressed in epinephrine equivalents. Since in the average case of pheochromocytoma a mixture of epinephrine and norepinephrine is excreted, it is not likely that any significant number of cases will be missed by this simplified technique.

Important to a satisfactory test is the proper preservation of the sample. Epinephrine is oxidized rapidly at a neutral or alkaline pH, and urine that stands in containers for even brief periods without being rendered acid may lose activity, particularly in the presence of metallic ions. On the other hand, when the sam-

ples are properly acidified the catechol amines withstand oxidation for long periods. An aliquot may be sent by mail, or it may be frozen, to be melted and analyzed at some later date. Details concerning the collection of urine samples and the method of chemical analysis used in our laboratory are given in Appendix 2, p. 253.

Interpretation of the results of such chemical tests is difficult, because of the infrequency of reported cases and the diversity of methods employed in studying them. However, certain generalizations are justified.

The level of total catechol amine excretion is above the upper limit of normal (100 to 150 μg. per 24 hours) in most cases of pheochromocytoma even when during the 24-hour interval the blood pressure is not elevated (Goldenberg, 1954). This may be explained by the efficacy of autonomic buffering mechanisms in preventing a rise in blood pressure despite the presence of supranormal amounts of circulating epinephrine. Such an inhibition of sympathetic vasomotor tone is suggested by the frequent finding in these cases of postural hypotension and impotence. Furthermore, the injection of epinephrine in a case of pheochromocytoma is associated with a less than normal rise in blood pressure, indicating that such inhibitory factors are present and active (Mayock, 1947).

When hypertension is continuously present, catechol amine excretion is consistently elevated in most cases. When hypertension is intermittent, the hourly rate of catechol amine excretion should be high during an episode of elevated blood pressure. However, spontaneous variations in the rate of excretion of these substances over short periods of time in the normal subject have not been well studied. A value exceeding 6 to 8 μg. per hour is probably sufficiently high to be diagnostic.

Some laboratories depend on analysis of blood levels of catechol amines for the detection of cases of pheochromocytoma, and a sensitive method has been devised for this purpose (Manger, 1954). Since no more than 3 to 4 per cent of epinephrine released into the blood can be detected in the urine, this method would appear to have advantages over the analysis of timed urine samples. However, the technique involves many practical difficulties: blood samples are more difficult to obtain

and preserve, and interpretation of the results of the chemical analysis is rendered uncertain by frequent false positive reactions. So long as experience continues to show a high frequency of positive results from urinalysis alone in cases of pheochromocytoma, use of another chemical screening method only complicates *matters without any apparent diagnostic advantage.*

BIOLOGICAL TESTS FOR PHEOCHROMOCYTOMA

Biological testing has been employed in many physiological laboratories and references to pertinent methods are supplied in the bibliography (Haimovici, 1952; Von Euler, 1953; Helmer, 1957). In general, these tests require considerable experience and are being supplanted by chemical analyses of urine or blood.

DIAGNOSTIC PROCEDURES DURING AN ATTACK

The most certain method of identification of pheochromocytoma as the cause of an attack of hypertension would be to examine the urine catechol amines during and immediately following an episode. Therefore, it is recommended that the patient be supplied with a bottle containing acid and instructed in the details of urine collection in the event an attack should occur. The instructions (specified in Appendix 2), are for the purpose of *collecting a measured urine sample over a specified time interval* during the attack. Should the analysis reveal a catechol amine excretion rate exceeding 6 to 8 µg. per hour, it is probable that an excessive epinephrine release has taken place. In addition to making arrangements for a urine collection, the patient or physician should be prepared to observe the pulse, blood pressure, and the presence or absence of cardiac irregularity (Table 3). The presence of hyperglycemia or glycosuria during an episode is of added help in making the diagnosis. Consequently, a blood sample should be drawn for glucose analysis or, if the attack occurs in the absence of a physician, a carefully measured portion of the urine sample can be submitted to analysis for glucose while the remainder is saved for chemical determination of catechol amines.

The effect of 2 5 mg. of Regitine given intravenously may be

TABLE 3. DIAGNOSTIC PROCEDURES TO BE PLANNED FOR ATTACKS

Physician, patient, or relative	*Physician only*
1. Note pulse rate and regularity.	1. Take blood sugar.
2. Observe color of skin, respiratory rate and depth	2. Take electrocardiogram.
3. Take blood pressure.	3. Give Regitine intravenously.
4. Collect quantitative timed urine specimen during attack* for sugar, catecholamines.	

* See Appendix 2 for details.

observed. This is one half the usual test dose, and if the diastolic blood pressure falls more than 20 to 25 mm. Hg there is little doubt that the episode is related to circulating epinephrine. The dose of Regitine may be increased if necessary to 5 and 10 mg. at 15- and 20-minute intervals, if the attack does not subside and if hypertensive symptoms are severe. While slow intravenous administration is preferable for test purposes, the drug is also effective when given intramuscularly in similar dosage, and may be preferred for the treatment of an acute attack.

RADIOLOGIC PROCEDURES FOR THE DIAGNOSIS OF PHEOCHROMOCYTOMA

Routine abdominal films or pyelograms may reveal displacement of the kidney, suggesting the presence of an adrenal tumor, particularly when the left kidney is lower than the right, an unnatural relationship in the normal state. An outline of the adrenal glands for the purpose of detecting enlargement may sometimes be achieved by presacral injection of gas; carbon dioxide is preferred to oxygen or air for this injection because of its high solubility in blood and the consequently reduced likelihood of serious gas embolism. When the gas is injected by the presacral route and followed by immediate filming in the upright posture, the renal and adrenal shadows are well visualized. The gas is absorbed with remarkable rapidity and the risk of serious gas embolism seems negligible, since the rapid removal of carbon dioxide from the lungs permits considerable amounts to enter the venous system without risk. This procedure is

useful in identifying the side on which the suspected pheochromocytoma is located. If such visualization reveals no adrenal tumor, surgery is still indicated if appropriate testing indicates the presence of a pheochromocytoma since some tumors may be too small to visualize by this method.

Aortograms are less likely to be diagnostic, since these tumors normally have few blood vessels. In several cases that were later proved to be pheochromocytoma at the University of Michigan Hospital aortograms were not helpful and had the further disadvantage of occasionally setting off an attack of hypertension.

MANAGEMENT BEFORE AND DURING SURGERY

Induction of anesthesia should be accomplished as smoothly as possible, since anoxia will frequently release epinephrine. The use of intravenous barbiturate with nitrous oxide and oxygen supplementation by the endotracheal route is recommended. Cyclopropane may potentiate arrythmias related to epinephrine release, while spinal anesthesia may magnify the degree of postoperative shock. Preoperative atropine or scopolamine should be used sparingly, since parasympathetic blockade may aggravate the response to epinephrine. The blood pressure should be monitored carefully throughout the procedure and a short-acting adrenergic blocking drug used only for extreme hypertension. Regitine intravenously is recommended although a number of other adrenolytic drugs have been used successfully. The blocking drugs should preferably have a short span of action so that little or no epinephrine inhibition will persist in the hypotensive period following removal of the tumor. For this reason dibenamine derivatives are not advised.

If the site of the tumor is not identified preoperatively, a bilateral exploration of both adrenal areas is preferred by some urologists, with two surgical teams working simultaneously. This reduces the time of operation and the anesthetic risk of two successive procedures and provides clear information concerning the presence or absence of a tumor in the areas in which it is most commonly found. If only one side is explored at a time, the right should be examined first, since tumors are more frequently

found on this side. Occasionally pheochromocytomas are found scattered along the abdominal or thoracic aorta. When the site is unknown, some authorities prefer the anterior approach, which permits a wider abdominal exploration.

Once the tumor is identified, the blood supply should immediately be clamped to prevent release of pressor material into the blood stream during operative manipulation. It is sometimes necessary to administer blood and norepinephrine or neosynephrine in very large doses to treat the shock that frequently follows excision of such tumors. The prophylactic use of adrenal steroids before surgery is probably advisable to insure against adrenocortical deficiency that might aggravate the postoperative shock. Despite the most careful management, irreversible shock or cardiac standstill is still a frequent complication of this operation.

Less than 10 per cent of the tumors are malignant; in these cases, however, metastasis may have occurred before excision. Occasionally, multiple pheochromocytomas are found. Postoperative testing will identify them. More puzzling are the cases of sustained hypertension that do not revert to normal blood pressure after complete removal of a tumor, despite cessation of the attacks. Even with occasional setbacks the discovery of a case of pheochromocytoma and the satisfactory relief that can be provided in a high percentage of these cases is one of the most gratifying experiences in the treatment of hypertension.

To illustrate the diagnostic management of cases presumed to be pheochromocytoma, the following case history from the records of the Hypertension Clinic is described (Hoobler, 1957).

Case History

A 32-year-old man was referred with the chief complaint of high blood pressure and "weak spells" of 18 months' duration. The latter came on suddenly and without warning, were associated with a throbbing headache, slowed pulse, a moderate rise in blood pressure, and frequent premature ventricular beats. During such attacks he became ashen gray and perspired profusely.

The physical examination on admission was normal except for

a blood pressure of 175/85 mm. Hg, which fell to 120/80 mm. on standing. It was reduced to 70/32 mm. Hg by 5 mg. and to 54/24 mm. by 2.5 mg. of Regitine intravenously. The benzodioxane test caused a fall of 28/18 mm. Hg. While the patient was in the clinic, a spontaneous rise in blood pressure to 242/104 mm. Hg occurred. To relieve the hypertension, 5 mg. of Regitine was given intravenously, resulting in a sudden drop in the blood pressure to 160/66 mm. Hg followed by a rebound rise to 300/142 mm., which soon decreased without further drug administration. The electrocardiogram during one previous mild attack had exhibited a marked sinus bradycardia, frequent premature ventricular beats, and large T waves suggestive of hyperkalemia. The basal metabolic rate was plus 15 per cent. Fasting blood sugars were 107–129 mg. per cent and the glucose tolerance test showed a diabetic pattern. Urinary catechol amine excretions in two 24-hour periods were 502 and 665 μg. per 24 hours respectively (normal 10–150 μg.). On bilateral adrenal exploration a tumor of the left adrenal gland was identified and removed without difficulty.

COMMENT. In addition to illustrating many of the points discussed in this chapter, this case exhibited an unusual feature in the paradoxical response to one injection of Regitine. It can only be presumed that, stimulated by the acute reduction in blood pressure, the tumor released into circulation more catechol amines than could be blocked by the drug.

SUMMARY

Pheochromocytoma must be excluded by pharmacologic testing in patients with hypertension. A screening test procedure is described, which involves injecting histamine when the pressure is below 200 mm. Hg systolic and Regitine when the pressure is above this level. Although most cases may be identified by testing with these drugs or their counterparts, urinary catechol amine excretion should be measured to confirm the diagnosis prior to surgery. In cases of intermittent hypertension, appropriate observations to be made in the home during an attack are described.



CHAPTER 3



"Curable" Hypertension of Adrenocortical Origin

Oversecretion of at least three adrenal hormones may be associated with hypertension; the relative amount of each determines the clinical picture that is likely to result. Although the androgenic hormone from the adrenal cortex (and sometimes from ovarian neoplasms) produces no hypertensive effect, moderate blood pressure elevation is occasionally seen in *congenital adrenal hyperplasia* caused by deficiency of the enzyme, 11-hydroxylase. The defect results in the synthesis of an abnormal pressor steroid resembling desoxycorticosterone. The condition occurs in children, is associated with precocious virilism, and is relieved by administration of the normal end-product of steroid synthesis, hydrocortisone (Conn and Fajans, 1957).

The glucocorticoids also have an effect on blood pressure and salt metabolism, which is more prominent when a renal lesion is also present (Knowlton, 1946). The clinical counterpart is seen when elevation of the blood pressure occurs in patients receiving cortisone for long periods, and especially in the treatment of lupus erythematosus complicated by a renal lesion. Consequently, it is not surprising that hypertension accompanies *Cushing's syndrome*, a condition associated with oversecretion of glucocorticoids, and that late in the disease, when renal insufficiency supervenes, severe hypertension and vascular disease are prominent. However, a diagnosis of the early form of Cush-

ing's disease should be considered in cases with mild blood pressure elevation. This condition may be recognized by the history of a recent shift of fat distribution to the face and neck, which leads to the development of a characteristic appearance. Other symptoms are amenorrhea, impotence, a decrease in muscle size, and the gradual development of weakness. A presumptive diagnosis can be entertained on the basis of careful observations during physical examination. Increased hair growth, a rounded and flushed face, acne, and purplish striae over the abdomen should lead the examiner to seek laboratory corroboration. Glycosuria or hyperglycemia, slight increases in the red or white blood cell count, and osteoporosis of the spine are further suggestive features. The eosinophil count is sometimes reduced but is more frequently in the low normal range. An increase in carbon dioxide-combining power with low serum potassium and high serum sodium levels are found in most cases, but an increase in urinary 17-hydroxysteroid excretion is necessary to confirm the diagnosis. The frequency with which these diagnostic features are encountered in Cushing's syndrome has been summarized by the Columbia University group (Plotz, 1952).

In some cases, hyperactivity of the adrenal cortex appears to be limited to oversecretion of aldosterone, a hormone with specific effects on electrolyte balance. In *primary hyperaldosteronism*, moderate blood pressure elevation is one of the few clinical manifestations of oversecretion of this steroid. However, the output of the hormone is also increased in nephrosis, cirrhosis, and congestive heart failure, conditions in which normal blood pressure levels frequently prevail. In essential hypertension aldosterone excretion may be normal or slightly increased. In Conn's original case (1955), a high level of urinary aldosterone was accompanied by only moderate hypertension The relation between aldosterone secretion and blood pressure elevation is, therefore, not clear.

Primary hyperaldosteronism is not yet understood well enough to establish reliable criteria for its distinction from some cases of hypertensive disease. The symptoms and diagnostic features that characterize the cases reported to date in the literature do not always follow a consistent pattern. The correct diagnosis may be suspected however, when there is a history of episodes of

TABLE 4. ADRENOCORTICAL HYPERTENSION

Characteristic features	*Diagnostic procedures*	
Hypertension plus	*First steps*	*Later steps*
Facies and obesity suggesting Cushing's syndrome	A. Glucose tolerance test B. Carbon dioxide combining power C. Red blood cell and eosinophil count	24-hour 17-hydroxysteroid excretion
Polyuria, polydypsia, episodes of muscular weakness, recurrent paresthesias, and tetany	A. Random urine neutral or alkaline B. Poor urine concentrating ability C. Low serum potassium, high carbon dioxide combining power	24-hour aldosterone excretion

weakness, and when polydipsia, polyuria, and nocturia are prominent. Intermittent paresthesias and tetany may occur with the attacks of weakness. Varying degrees of blood pressure elevation and of secondary vascular changes in the heart and retina may be found, but the physical examination is not otherwise helpful. Edema is not usually present. The urine is frequently neutral or alkaline and of low specific gravity even after dehydration. A high serum sodium level or plasma carbon dioxide combining power or low serum chloride may furnish additional assistance. The most significant laboratory finding is a serum potassium below 3.5 mEq. in the absence of prior chlorothiazide therapy. However, the concentration of potassium is not always reduced except during an episode of muscular weakness. Furthermore, a low blood level may be elevated by a high potassium intake or may go unrecognized because of a slight hemolysis of the blood sample. The diagnosis of primary hyperaldosteronism cannot be made in every case even after aldosterone excretion has been measured. Differentiation from other forms of hypertensive disease will continue to be difficult, since some hypertensive patients may exhibit a moderate hyperexcretion of aldosterone (Genest, 1956), and edema secondary to hypertensive, cardiac, or renal disease is also characterized by an increase in aldosterone secretion.

Despite these difficulties, primary hyperaldosteronism can usu-

ally be excluded with reasonable certainty if every hypertensive patient is carefully examined with respect to urinary pH and concentrating power, and if a serum potassium measurement is performed. In the absence of such examinations, many cases of primary aldosteronism may go unrecognized in practice. This possibility is illustrated by two cases described by Dr. James Hewlett (1957) in which hypertension was one of the chief presenting features. A clinical résumé of one of these cases is presented below.

Case History

A 44-year-old man was admitted to the Cleveland Clinic complaining of polydipsia and nocturia for 3 years. He had had recurrent spells of muscular weakness for several years and hypertension since the age of 19. His blood pressure on admission was *200/128 mm. Hg. There was moderate retinal arterial constric*tion. The physical examination revealed no other abnormality. The urinalysis was normal, but the specific gravity did not exceed 1.016. Urinary pH did not fall below 7.0. Urea clearance was normal Serum sodium and potassium determinations varied from 140–148 mEq. and 2.6–3.0 mEq per liter respectively. The carbon dioxide combining power was high (32.5–35.8 mEq.). The amount of aldosterone excreted in 24-hours was 23.5 μg., compared to an upper normal value of 6 μg. After removal of an adrenocortical adenoma the patient's blood pressure fell gradually to 148/100 mm Hg within the course of one month. The symptoms were relieved and the serum electrolyte abnormalities disappeared.

COMMENT. This patient appeared to have had typical long-standing benign hypertension, until he had noticed symptoms which to the Clinic physicians suggested hyperaldosteronism Once the condition was suspected, a diagnosis was readily made by appropriate laboratory tests.

SUMMARY

Hypertension is frequently associated with adrenocortical hyperfunction. Cushing's syndrome can generally be recognized by

the characteristic appearance of the patient and the coexistence of diabetes, osteoporosis, hyperkalemic alkalosis, and other features. Urinary 17-hydroxysteroid excretion is increased. Hypertension caused by primary hyperaldosteronism is more difficult to recognize; a serum potassium determination should be performed particularly if there is evidence of polyuria, polydipsia, and intermittent episodes of muscular weakness.



CHAPTER 4



"Curable" Hypertension: Coarctation of the Aorta

Coarctation of the aorta should be suspected in all young adults with mild elevation of the blood pressure. The diagnosis should also be considered when the patient gives the history that his "blood pressure has always been elevated a little" or when he states that he has noticed weakness in the posterior thigh muscles on activity. Intermittent claudication, as manifested by pain in the calf on exercise, is a less common complaint, presumably because the collateral circulation to this region is superior to that in the thigh.

In the course of the physical examination the physician may hear a systolic murmur of more than minor degree at the base of the heart. He may note that the femoral pulse is absent or weaker and delayed when compared with the radial pulse. Pulsation in the dorsalis pedis or posterior tibial arteries is also frequently absent. Auscultation over the scapular regions or between the intercostal spaces may yield evidence of a short systolic murmur as blood courses through the intercostal anastomoses.

When a pulse is felt in the femoral region, it is invariably delayed. Sir Thomas Lewis (1933) has explained this finding as the result of summation of many different collateral pulses that reach the femoral artery at slightly different times, thus creating a more rounded pulse wave, the peak of which is substantially

delayed. In the normal individual, radial and femoral pulses are by contrast felt simultaneously by the palpating finger. A delay in the arrival time of the femoral pulse is of diagnostic value even when a good femoral pulse is palpable (Friedenberg, 1946).

A more certain method of identifying coarctation consists in determining arm and leg blood pressures in every patient with hypertension. In some cases of coarctation the blood pressure in the legs may be only slightly below that in the arms and its determination by the conventional method may be subject to considerable error. This method, which consists of inflating the cuff on the thigh and listening for the Korotkoff sounds in the popliteal area, is often unsatisfactory. Furthermore, an especially wide cuff must be used to secure an accurate reading. Abnormally high readings will be obtained if a standard width cuff is used, since to occlude the artery such a cuff must be inflated to a higher pressure because of the large muscle mass at the thigh that must be compressed. Because of this error the physician may miss a small differential between leg and arm blood pressure. However, a cuff of standard width may be wrapped around the calf, a portion of the lower extremity the circumference of which is closer to that of the upper arm. The appearance of a palpable pulse over the dorsalis pedis or posterior tibial artery on deflation is then used to determine the systolic pressure in the legs.

If the physical findings are suggestive of this condition x-ray examination of the chest should be performed. Notching of the ribs, a visible aortic deformity on the film, or deviation of the esophagus noted on swallowing barium during fluoroscopy will serve further to confirm the diagnosis (Figley, 1954). The precise extent and severity of the coarctation can be determined by angiocardiography.

DIFFERENTIAL DIAGNOSIS AND TREATMENT OF COARCTATION

Coarctation may appear in a variant form in which the congenital narrowing is in the abdominal aorta at or near the orifice of the renal arteries. In this case, the hypertension will be less

severe and the evidence of collateral flow in the thorax less prominent (Bahnson, 1949). A systolic murmur may be heard over the upper abdomen, and the aortic pulse usually felt in the epigastrium will be missing.

TABLE 5 AORTIC COARCTATION

Clinical status	*Chief physical signs*	*X-ray confirmation*
Young patient	Absent or weak pulse in the feet	Rib notching on chest film
Mild hypertension	Delayed arrival of pulse wave in femoral artery	Esophageal deviation with barium swallow at fluoroscopy
Fatigue of thigh muscles on exertion	Systolic blood pressure in calf determined by palpation to be distinctly lower than brachial blood pressure	Angiocardiogram to determine further details

In every hypertensive patient one should verify the presence of a good femoral pulse arriving at the examining finger synchronously with the radial pulse, or the blood pressure in legs and arms should be determined.

Aortic thrombosis may be confused with coarctation of the aorta. Although the former condition appears in more elderly patients, resemblances to coarctation include the symptoms of weakness about the thighs on activity, the absent, weakened, or delayed pulses in the lower extremities, mild blood pressure elevation, and coincidental cardiac murmurs. However, the history of the onset of the hypertension or of the disability of the legs in late middle life suggests aortic thrombosis. Furthermore, since the obstruction frequently involves the iliac arteries to a different degree on the two sides, differing blood pressure readings may be obtained in the two legs. Finally, the roentgenologic findings of coarctation are absent.

Angiocardiography serves to localize the point of coarctation Owing to the poor prognosis in the usual form of this condition (Reifenstein, 1947), surgical correction is advised. After excision of the coarctation, the accessory signs and symptoms disappear with gratifying rapidity, although in some cases the hypertension does not subside completely. Aortic angiograms have identified cases of partial coarctation or of coarctation so well compensated

by collateral circulation as to present very little evidence of hypertension and correspondingly little risk to life. In other cases a major branch of the aorta may be involved in the process. Even in these cases there occurs some risk from poststenotic dilatation and aortic rupture. While surgical excision of the lesion is not now recommended for such patients, improvement in techniques may hasten the time when all individuals with coarctation will be recommended for surgical treatment regardless of location, age, degree of narrowing, or blood pressure.

SUMMARY

In coarctation of the aorta, the diagnosis is made on the basis of a reduced blood pressure in the legs, the delayed arrival of the pulse wave in the femoral artery, and other features. Treatment consists in excision of the anomaly.

SECTION II

SECONDARY HYPERTENSION NOT SUSCEPTIBLE TO CURE



CHAPTER 5



Bilateral Renal Disease

Many cases of hypertension in which the cause may be identified originate from various lesions of the kidney. Page and Corcoran (1949) list 28 separate morbid conditions affecting this organ that may be associated with hypertension. Unfortunately, since most of these conditions are bilateral it is impossible to cure the hypertension by nephrectomy.

ACUTE GLOMERULAR NEPHRITIS

Diagnosis

The course of acute glomerular nephritis was vividly described by Addis (1949). The renal lesion commonly manifests itself by gross or microscopic hematuria associated with elevation of the blood pressure. The disease runs a self-limited course, healing completely in the majority of cases in childhood but in fewer cases in adult life. Sometimes it is difficult to differentiate malignant hypertension with gross hematuria from an unusually severe acute nephritis unless an antecedent history of hypertension is obtained. In acute nephritis cardiac and encephalopathic symptoms occur at lower blood pressure levels, edema is more prominent, and spontaneous improvement is common.

The streptococcus group 12 has been indicted as nephritogenic in the majority of cases described by Rammelkamp and his collaborators (1953). In an extensive study of persons exposed to

infection with these streptococci, the renal lesions were shown to occur frequently without any clinical manifestation (Rammelkamp, 1955).

Control of the Blood Pressure

Encephalopathy, congestive failure, and azotemia occur in acute nephritis at levels of blood pressure that most patients with chronic essential hypertension withstand for years without difficulty. Therefore, treatment must be started at a lower level of blood pressure than in essential hypertension, if complications are to be avoided. For these reasons, it is well to provide mild suppressive treatment with oral and parenteral reserpine, if in a case of acute nephritis the blood pressure rises above 160 mm. Hg systolic or 110 mm. diastolic. The use of chlorothiazide might also be considered although its effects in this disease are not yet fully known. Vigorous forms of drug treatment, such as with mecamylamine, should be advised if the systolic blood pressure exceeds 190 to 200 mm. Hg.

A convulsive seizure may be the first apparent reaction to the hypertension. Magnesium sulfate given intramuscularly is helpful in treating such a manifestation of encephalopathy or in preventing its recurrence, especially in children (Burke, 1958). If there is no anuria, 0.1 ml. of a 20 per cent solution per kilogram of body weight may be given intramuscularly every 6 to 8 hours. The blood pressure should be followed with great care. It seems probable that reduction of the blood pressure is the chief factor in preventing recurrent convulsions and in decreasing the likelihood of pulmonary edema. A variety of hypotensive agents, such as rauwolfia, veratrum, and magnesium sulfate, have all proved helpful.

Such a reduction in blood pressure probably has little effect on the course of the underlying renal lesion. On some occasions antihypertensive treatment may lead to a transient rise in blood urea levels although this increase may also occur spontaneously if the disease worsens. Careful judgment is necessary in the use of hypotensive drugs since too great a depression of the blood pressure may aggravate the acute renal failure. A good therapeutic goal would be to reduce the blood pressure no more than 20 to 40 mm. Hg.

ACUTE POSTINFECTIOUS HYPERTENSION

Reubi and his co-workers (1953) have identified a form of apparent infection without hematuria, in which cyclic changes in renal blood flow were associated with mild hypertensive episodes. The following case may have presented some features of this unusual condition.

Case History

The patient, a 24-year-old woman, had experienced an episode of anorexia and lassitude 8 weeks before her first admission to the hospital. Two weeks later she was examined in the Admitting Clinic because of sore throat and backache. At that time her pharynx was slightly congested and there were signs of coryza. Hospital records showed that during late pregnancy, two years before and again one year before, the patient's blood pressure levels had been 140/90 mm. and 158/94 mm. Hg. During the two weeks following her visit to the Clinic she suffered recurrent attacks of severe vomiting and headache; it was found that her blood pressure was elevated, and she was admitted to the hospital.

On admission the patient's blood pressure was 190/120 mm. Hg; there was no fever. Focal retinal arterial vasoconstriction, early blurring of the disc margin, and one small exudate were noted. Blood studies revealed no abnormality. Of the 5 urine specimens examined, one showed 1-plus albumin and one, a trace. Specific gravity of these samples varied from 1.010 to 1.020. In the first 15 minutes 31.6 per cent of injected phenolsulfonphthalein was excreted. Creatinine clearance, nonprotein nitrogen, and C-reactive protein determinations were normal. Intravenous and retrograde pyelograms demonstrated no abnormality of the kidneys. Two Regitine tests were negative.

The blood pressure remained in the range of 180/130 mm. Hg to 200/140 mm. for the first 3 days following the patient's admission. Thereafter, treatment with rauwolfia alkaloids, together with rest in the hospital, resulted in a gradual decline in blood pressure to upper normal levels after 10 days Six months later she developed a recurrence of nausea and vomiting and was

found to have a mild recurrence of the hypertension and to be two months pregnant. The patient had a spontaneous abortion and the symptoms subsided. For two years her blood pressure rarely exceeded 150/90 mm. Hg, although at the completion of a normal full term pregnancy one value of 190/104 mm. was recorded. On the occasion of a recent attack of pharyngitis the blood pressure reached 180/110 mm. Hg. The urinalysis was normal. With recovery, the pressure again fell to normal.

COMMENT. This young woman has had a high normal blood pressure for some years. After an attack of pharyngitis she showed some of the features of early malignant hypertension, but urinalyses revealed nothing except slight albuminuria. The blood pressure has remained normal for several years except for a rise following another transient attack of pharyngitis. While the relationship between the throat infections and the hypertensive episodes is conjectural, the occurrence of an "acute infectious hypertension" was considered as a possibility.

CHRONIC GLOMERULAR NEPHRITIS

Diagnosis

The moderate elevation of the blood pressure seen in chronic glomerular nephritis is rarely a matter of much concern during the long latent or subacute phase of the disease. Terminally, the blood pressure becomes markedly elevated and may take precedence as the disturbance that immediately threatens the patient's life. In this phase, chronic nephritis may closely resemble malignant hypertension with azotemia. In the absence of a history of proteinuria preceding the onset of severe hypertension, differentiation is difficult. In chronic nephritis there is a greater degree of albuminuria, hematuria, and casts. The nonprotein nitrogen is more markedly elevated while anemia, hypoproteinemia, and edema are further indications that the disease is of primary renal origin. By special renal function tests it is possible to show that the filtration fraction is reduced in chronic nephritis with secondary hypertension, whereas it is elevated in malignant hypertension (Corcoran, 1944).

Control of the Blood Pressure

There is little one can do to modify the course of chronic nephritis. The treatment of the renal insufficiency is discussed elsewhere (p. 165). The evolution of the disease is probably not altered by treatment, but death may be postponed. When the blood pressure has exceeded a substantial level, the physician *may well attempt some degree of control. No specific recom*mendation may be given, however, in the absence of answers to these questions: How much does the hypertension itself add to the deterioration of the kidney in chronic nephritis? Does control of a moderately elevated blood pressure in this condition prolong *survival? Regardless of how much the blood pressure is reduced,* the disease will probably continue its inevitable course. Consequently, treatment for asymptomatic hypertension should be prescribed with considerable hesitation. When, however, symptoms related to hypertension are clearly disturbing to the patient, a *different strategy is justified. For example, more rigorous* treatment regimens may be prescribed if the head-up bed and chlorothiazide or salt restriction do not relieve the headaches, if the use of digitalis and restriction of activity do not improve congestive heart-failure, and if fresh retinal hemorrhages or exudates threaten to impair vision. When these last mentioned symptoms occur, the blood pressure is usually considerably elevated and the nephritic process has passed to its terminal phase of renal insufficiency. To embark on antihypertensive therapy at such a stage is to take a certain calculated risk. Reductions of perfusion pressure in the kidney will inevitably accelerate, at least transiently, the degree of renal excretory failure already present But if such measures bring relief of symptoms to a patient who is in any event drifting toward a fatal termination, then the treatment is justified. An individual with chronic nephritis tolerates considerably more azotemia than a hypertensive patient. One may therefore justifiably choose to lower the blood pressure even in the presence of nonprotein nitrogen levels of 100 to 150 mg. per cent, whereas in the patient with primary hypertension such treatment usually ends disastrously.

The following rules represent the current practice of our clinic

in controlling the blood pressure in chronic nephritis. When the levels consistently exceed 180 mm. Hg systolic in the asymptomatic patient, rauwolfia is prescribed for an indefinite period if blood pressure reduction can be assured without prominent side effects. Above the level of 200 mm. Hg a ganglion-blocking agent, usually mecamylamine, is introduced. The objective is to achieve a moderate reduction of the systolic standing blood pressure to the range of 160–180 mm. Hg in order to prevent vascular damage to the kidney without precipitating further renal failure or producing serious drug-induced side effects. Despite the reduced glomerular filtration rate associated with chlorothiazide, the drug has been safely administered to nephritic patients and may also be useful in chronic nephritis with hypertension. If the nonprotein nitrogen exceeds 80–100 mg. per cent, mecamylamine tremor may develop (Perry, 1957a). If this occurs, low doses of pentolinium or chlorisondamine (Ecolid) should be tried, but with caution since a very small amount of the drug is effective in the presence of renal failure. If the nephritic patient is without symptoms but tolerates these drugs poorly, it may be best not to pursue further therapeutic attempts, reserving the use of these drugs or of reserpine in parenteral forms only for cardiac, retinal, or encephalopathic complications.

A dramatic cure of hypertension and renal insufficiency has been reported by Merrill, Murray, Harrison, and Guild (1956) in a case of chronic nephritis with malignant exacerbation. In this patient it was possible to introduce a viable renal transplant from an identical twin with alleviation of the renal insufficiency. Blood pressure fell, but not to normal levels. Subsequent removal of both diseased kidneys accomplished an apparent cure. This case demonstrates that there are probably two aspects to malignant hypertension of apparent renal origin. In the first place the presence of normally functioning renal tissue prevents the malignant state from developing while secondly the diseased kidney contributes in some way to the hypertension. This may explain why the malignant syndrome occurs only when renal insufficiency supervenes and why only mild forms of hypertension are seen in primary renal disease with adequate renal function.

CHRONIC PYELONEPHRITIS

The studies of Weiss and Parker (1940) and of Longcope (1937) indicate that at least in the terminal phase of chronic pyelonephritis a serious hypertension frequently but not invariably develops. Furthermore, as noted previously, unilateral chronic atrophic pyelonephritis may lead to long-standing hypertension as demonstrated by blood pressure reduction following nephrectomy. There is considerable controversy concerning the early recognition and diagnosis of this condition and its importance as a potential cause of serious hypertension. The high incidence of pyelonephritis, as confirmed at autopsy in cases of malignant hypertension, is a reminder that renal infection may precipitate a fatal malignant course in cases of otherwise relatively benign hypertension. On the other hand, chronic pyelonephritis may sometimes terminate in uremia without hypertension. The factor in this process that excites the hypertensive response has not been identified.

Diagnosis and Treatment

The diagnosis of chronic pyelonephritis can rarely be made on the basis of the history or physical examination, but depends on repeated urine examinations or renal biopsy. White blood cells in the urine of patients of either sex must be viewed with suspicion, if they stain characteristically by the Sternheimer technique (1951), they are more likely to be of a pyelonephritic origin. When this condition is suspected, a cleanly voided fresh sample should be obtained and a quantitative urine culture performed. This technique (MacDonald, 1957) has the advantage of distinguishing truly pathogenic organisms from frequent contaminants and of indicating the magnitude of the infection. After the sample is taken, the patient may be given sulfisoxazole (Gantrisin) 0.5 Gm. four times daily or sulfamethoxypyridazine (Kynex) 0.5 Gm. twice daily, and directed to return in one to two weeks for re-evaluation. If the infection is still present, specific treatment may be prescribed according to the result of sensitivity tests performed on the organisms cultured from the previous urine specimen. Careful surveillance of the urine should be part of the routine follow-up in all cases of hypertension,

particularly when urinary tract symptoms are present, renal function is critically impaired, or blood pressure levels are greatly elevated.

Every patient with a persistent or recurrent urinary infection should also undergo a careful examination for obstructive disease first by intravenous pyelograms and then, if necessary, by retrograde methods. No obstructive lesion likely to encourage pyelonephritis should be allowed to remain, particularly when retrograde examination indicates a unilateral source of infection. Renal biopsy, while admittedly showing occasional parenchymal inflammatory foci not detectable in the urine, may also miss these areas. It is not routinely recommended despite an occasional diagnostic or therapeutic success (Kark, 1955).

Significant hypertension does not usually appear during the acute, subacute, or early recurrent stages of pyelonephritis. The importance of recognizing and treating these conditions lies chiefly in the hope of preventing focal scarring with terminal renal insufficiency and hypertension. When pyelonephritis becomes chronic and destroys renal tissue to the point of inducing azotemia, severe, frequently malignant hypertensive disease commonly results. It appears that as in chronic glomerular nephritis a sudden malignant exacerbation of the hypertension is likely to occur in the terminal stage, particularly if the scarring from the inflammatory tissue involves predominantly the renal arterioles. At this final point in its evolution, chronic pyelonephritis is usually characterized by small renal shadows on x-ray, relatively slight proteinuria, often without pyuria or a positive urine culture.

Chronic pyelonephritis, malignant hypertension, and renal excretory failure may be prevented if the infection is recognized and treated in the early stages. Such a preventive program includes removal of any obstructive lesion, continuous supervision of the urine for the presence of leukocytes and pathogenic organisms, and when these are found the application of a more or less continuous antibiotic program. If the physician were to take the attitude "once a pyelonephritic, always a pyelonephritic," and keep such patients under constant supervision, he would see fewer cases of terminal pyelonephritis with irreversible hypertensive disease.

Control of the Blood Pressure

In chronic bilateral pyelonephritis antihypertensive treatment should conform to the principles applicable to chronic nephritis (p. 43).

POLYCYSTIC DISEASE OF THE KIDNEY

This condition rarely leads to a severe or malignant form of hypertensive disease despite presumably great increases in intrarenal pressure, together with renal excretory insufficiency, a combination that leads to severe hypertension in the experimental animal. Perhaps this condition should be classed rather in the category of lesions that have avoided hypertension by so-called autonephrectomy as is the case, for example, when with complete obstruction of the ureter renal functional tissue is totally destroyed without a trace of hypertension.

VASCULAR DISEASE INVOLVING BOTH KIDNEYS

Among the generalized vascular diseases that commonly involve the kidneys and may give rise to secondary hypertension are polyarteritis nodosa and generalized lupus erythematosus. The blood pressure should be controlled for symptomatic relief alone, using the principles outlined for chronic nephritis. Generalized arteriosclerosis may produce a *bilateral renal arterial obstruction* with hypertension. An ascending thrombosis of the aorta, as in the Leriche syndrome, may lead to renal arterial obstruction with secondary hypertension.

OBSTRUCTIVE LESIONS OF THE KIDNEY AND URETERS

A slow, gradually progressive ureteral obstruction may be an occasional cause of severe or malignant hypertension. Abrupt ligation of the ureter, on the other hand, rapidly causes hydronephrosis and destruction of the kidney tissue without hypertension. Partial ureteral obstruction such as that caused by renal calculi or an aberrant renal vessel may or may not result in a rise

in blood pressure. It would seem that a certain degree and duration of the ureteral obstruction are necessary to produce hypertension. Several situations in which this may occur have already been discussed (p. 5). The report that follows describes one such case.

Case History

A 45-year-old housewife was admitted to the hospital with complaints of occipital headaches, nausea, and vomiting of 6 weeks' duration. Just before admission she had had a sudden loss of vision and a generalized convulsion. One year previously she had undergone a resection of the sigmoid colon for carcinoma. No hypertension was noted at that time.

On admission examination the patient appeared comatose and had a blood pressure of 240/120 mm. Hg. The left fundus contained several soft exudates but there was no evidence of papilledema or of focal retinal arterial vasoconstriction. Several masses were felt on pelvic examination that suggested carcinomatous implants. The blood nonprotein nitrogen was 210 mg. per cent. A normal volume of urine was passed daily and 5 to 7 red blood cells per high power field were found in the sediment. Retrograde examination revealed a left hydronephrosis with narrowing of the left ureter at the level of the 4th lumbar vertebra. The right ureter was obstructed at the pelvic brim. A left nephrostomy was performed and the blood pressure fell to 120/80 mm Hg, remaining at this level until the patient was discharged. The blood nonprotein nitrogen was reduced to 96 mg. per cent and the patient left the hospital much improved.

Seven months later she was readmitted to the hospital. At this time the nonprotein nitrogen was 26 mg. per cent and the blood pressure was 120/80 mm. Hg, but the carcinoma had spread and a colostomy was necessary. She died 3 months later without a recurrence of hypertension.

COMMENT. This is one of several cases in which the abrupt onset of extreme hypertension and uremia has been associated with partial bilateral ureteral obstruction in the absence of oliguria. In this instance it was presumed that recurrent carcinoma had

caused the ureteral obstruction. The rapid relief of the hypertension and the improvement in renal function after nephrostomy were gratifying aspects of the case.

SUMMARY

Many renal diseases may cause hypertension. Those outlined in this chapter cannot be "cured" because they are bilateral. In acute nephritis, often caused by a nephritogenic strain of streptococcus, antihypertensive therapy may be required to forestall or treat emergencies such as encephalopathy and cardiac failure. The ability of blood pressure reduction to prolong life in chronic nephritis is debatable, but such treatment is advisable when symptoms caused by hypertension are present The diagnosis and chemoprophylaxis of pyelonephritis is stressed because of its importance in preventing the late development of malignant hypertension. Attention is called to the exceptional case in which chronic partial obstruction of ureteral flow may induce a temporarily reversible hypertension.



CHAPTER 6



Hypertension With Diseases of the Heart and Large Arteries

Blood pressure depends on three interrelated variables: stroke volume of the heart, peripheral resistance, and aortic elasticity. With the fluctuations in cardiac output and peripheral resistance that follow digestion, emotional reactions, and activity, it is indeed impressive that the blood pressure is maintained relatively constant. With aging, aortic elasticity decreases and this is the most likely cause of the increasing systolic blood pressure of persons as they grow older (Master, 1950). In this chapter will be reviewed the effects on the blood pressure of changes in cardiac output and arterial elasticity.

CONDITIONS AFFECTING THE BLOOD PRESSURE THROUGH ALTERATIONS IN STROKE VOLUME OF THE HEART

Anyone who has taken the blood pressure in a patient with auricular fibrillation will be impressed with the effect of stroke volume on both the systolic and diastolic blood pressure. In this condition peripheral resistance remains reasonably constant, and pressure fluctuations represent variations in output of blood per heart beat. If ventricular filling time is prolonged and a large amount of blood must be ejected, the systolic pressure will rise markedly and the diastolic slightly. This is an example of the

effect of increased stroke volume on the systolic blood pressure. Large stroke volumes also occur after exercise and in hyperthyroidism. The hypertension in these situations is usually mild because there is concomitant peripheral dilation. Nevertheless, the diagnosis of *thyrotoxicosis* must sometimes be considered in young people with mild hypertension. Although essential hypertension may elevate the basal metabolic rate slightly, it does not alter the iodine metabolism. In *heart block* with a slow ventricular rate and a large stroke volume, the systolic blood pressure may be greatly elevated. In one case, that of an elderly gentleman who was examined in the Hypertension Clinic, the readings exceeded 300 mm. Hg systolic and 110 mm. diastolic. This resulted from a very slow pulse rate, an increase in stroke volume, and a loss of aortic elasticity. While hypertension of this variety is easily identified, *aortic insufficiency* is sometimes more difficult to recognize. Here, of course, the very large stroke volume is necessary to maintain adequate forward flow in the presence of aortic regurgitation with each diastole. The classical case of aortic insufficiency can be recognized by the presence of an aortic diastolic murmur, the characteristic peripheral pulse, the elevation of systolic pressure in the legs when compared to the brachial readings, and the history of syphilis or rheumatic fever. *The diastolic pressure is usually not elevated.* In such cases effective antihypertensive measures may provide considerable symptomatic relief.

In rare instances a hypertensive patient may develop an aortic diastolic murmur. In this situation one must assume a dynamic dilation of the base of the aorta, since at autopsy the aortic valves usually appear to be intact. Reduction of the blood pressure often results in reduction or elimination of the diastolic murmur.

HYPERTENSION SECONDARY TO DECREASED ARTERIAL ELASTICITY

The role of decreased vascular elasticity in causing or maintaining essential vascular hypertension as well as in so-called arteriosclerotic hypertension is a much neglected subject. Wiggers (1932) was the first to show that the wave transmission characteristics of the arterial wall were altered in essential hyper-

tension. Recent studies of the changes in elasticity of the arterial wall and of the carotid sinus area in experimental and in human essential hypertension indicate the possible part which these factors might play in the maintenance of hypertension (McCubbin, 1958). The steady increase in systolic blood pressure in the older age groups suggests that this change in the elasticity of large arteries is also a characteristic of senescence. This change with age must vary among individuals and depend on hereditary endowment. To this extent, a large number of older persons with moderate hypertension may be, in fact, individuals with a familial predisposition to a more than normally rigid vascular tree.

It is readily apparent that no sharp distinction can be drawn between the so-called arteriosclerotic and other varieties of hypertension. However, since prognosis and management differ somewhat, the following working definition is proposed: Arteriosclerotic hypertension is that form of blood pressure elevation which results from large-artery sclerosis rather than from an increase in peripheral resistance. It is characterized chiefly by systolic hypertension, the diastolic pressure never exceeding 110 mm. Hg and usually being lower. It is seen after the age of 55 in otherwise normal persons, and before this age in diseases commonly associated with premature arteriosclerosis such as diabetes and myxedema.

Such individuals will comprise a large proportion of the elderly hypertensive population as well as almost all those with diabetes of 10 to 15 years' duration, particularly those with diabetic nephropathy. As might be expected, the blood pressure in these patients varies more markedly with alterations in the volume of blood contained in their arterial system whether such alteration be due to entrapment by arteriolar constriction, to overfilling by increases in cardiac output, or to blood loss into the peripheral venous pool as a consequence of depressor drugs. Therefore, when emotional stimuli constrict the arterioles or raise the stroke volume, excessive rises in blood pressure follow. These patients are thus possessed of a very labile blood pressure as a result of increased arterial rigidity. It is as if the modulating influence of the large arterial reservoir, the "Windkessel" of the German authors, has been lost so that its homeostatic influence is no longer

exerted to maintain the blood pressure during extremes of vasomotion or stroke volume deviation.

The prognosis of arteriosclerotic hypertension is poorly understood. It has been commonly accepted that the great majority of such persons live out a normal life span. Treatment should consist of mild measures such as reassurance and small doses of chlorothiazide. Reserpine should be prescribed with some care, in view of the frequency of involutional depression in this age group and the attendant risk that reserpine-like drugs may bring these symptoms to the fore. Even when this regimen is ineffective, it is best to avoid ganglion blocking agents unless there is clear evidence that the blood pressure elevation may be responsible for some of the patient's symptoms or findings. An elderly individual with this form of hypertension who is having morning headaches or paroxysmal nocturnal dyspnea might be tried on a cautious program of ganglion blocking agents if the systolic blood pressure exceeds 200 mm. Hg and is unresponsive to milder agents. The modified treatment regimen suggested (Appendix 7, p. 282), might be preferred to a more vigorous program.

Treatment of Arteriosclerotic Complications of Hypertension

A few complications in the arteriosclerotic hypertensive patient call for stricter control of the blood pressure. These include serious hypertensive retinopathy, aneurysms, and focal cerebrovascular episodes associated with a hypertensive crisis. When vision is threatened by *retinal arterial lesions,* careful blood pressure reduction may be helpful. The following cases from our clinic records illustrate some of these points.

Case History

A 55-year-old-woman was referred to the Hypertension Clinic because of hypertension and failing vision. Three months previously she had experienced sudden loss of vision in the left eye, and a diagnosis of retinal vein thrombosis had been made. At the time the patient entered the hospital a similar but less extensive accident had occurred in the right eye, and after several weeks of observation, the lesion appeared worse and vision was progressively failing. The blood pressure varied between 190/113

mm. and 231/128 mm. Hg. There were no other manifestations of cardiovascular or renal disease. The patient was treated vigorously with ganglion-blocking agents during the following 3 years and her blood pressure has been well controlled with frequent readings as low as 100/70 mm. Hg. Her vision improved considerably within a few days after treatment was begun, and has remained satisfactory except for two brief episodes of vitreous hemorrhage.

COMMENT. Reduction of the blood pressure was instituted to prevent further retinal vascular disease. This was done without great expectation of success, but because no other treatment had succeeded in arresting her progressively failing vision. She had experienced two serious retinal vascular accidents during 4 months of uncontrolled hypertension and no episodes during three years of effective blood pressure control. Antihypertensive treatment may have favorably affected the spontaneous course of her illness.

Large *aneurysms* of the aorta and perhaps of the cerebral arteries are occasional consequences of generalized arteriosclerosis. If the lesions are not amenable to surgical attack, reduction of the blood pressure in cases with severe systolic hypertension may well prolong life. In patients with such lesions vigorous antihypertensive treatment should be encouraged in order to keep the blood pressure at the lowest possible level that can be tolerated. Decompression of the aneurysm by reducing intra-arterial pressure may give rise to immediate and gratifying improvement such as was experienced in the following case.

Case History

A 53-year-old woman was admitted to the hospital with a history of attacks of severe left periorbital headaches and diplopia of 4 days' duration. She had had known hypertension for 15 years with recent systolic readings above 220 mm. Hg. Examination revealed ptosis of the left eye and evidence of paresis of the left third cranial nerve. The blood pressure was 208/108 mm.

Hg. Treatment with hexamethonium bromide, 5 mg. subcutaneously every 4 hours, produced marked symptomatic relief and lowered the systolic blood pressure to 160 mm. Hg for a few days. When treatment was discontinued, the blood pressure rose to 200/140 mm.; the pulsating left periorbital headache and oculomotor paralysis reappeared, subsiding again when treatment was resumed. The patient was discharged with a presumptive diagnosis of an aneurysm of the left internal carotid artery with pressure on the third cranial nerve.

COMMENT. While no cerebral angiograms were made to establish the diagnosis, the unilateral throbbing character of the headache and the reversible neurological lesion suggested pressure on neighboring structures and indicated a possible aneurysmal dilation of the left internal carotid artery. The diagnosis was further supported by the relief of pain and of the signs of compression each time the blood pressure was lowered.

The more closely patients with arteriosclerotic hypertension are observed, the less certain it is that their course is benign. While they must carry at least the same risk of a vascular complication as normotensive older persons, clinical experience suggests that even transient elevations of blood pressure may in themselves contribute to a *cerebrovascular catastrophe*. The following case history illustrates this point.

Case History

Referral opinion was requested on a 65-year-old woman with [illegible] office [illegible] The [illegible] became ill and died. Shortly after the funeral the patient noted the onset of left hemiparesis and visual difficulty. She was admitted to the hospital, and at that time a blood pressure of 230/120 mm. Hg was recorded Reserpine was given, 0 25 mg three times daily, and when the patient was discharged 10 days later the blood pressure was again 150/90 mm. and partial neurologic re-

covery had occurred. Three weeks later her blood pressure was 130/86 mm. Hg; there were hyperactive reflexes on the left side and left homonymous hemianopsia. Drug therapy was gradually discontinued. The pressure 2 months later was 142/88 mm. Hg and the patient had gradually resumed normal activity.

COMMENT. Before the occurrence of the cerebrovascular episode, this patient would have been given an excellent prognosis. The cerebral attack appeared to bear some relation to the extreme emotions engendered by her mother's funeral. Although the unusually high blood pressure recorded immediately after the attack could have been caused by anxiety about her condition, occasional experiences with other patients have demonstrated that such acute pressor episodes may precede cerebrovascular accidents by several hours. It is likely that in this case the acute hypertension provoked the cerebrovascular "spasm." Certainly, there is little reason to implicate hypotension and cerebrovascular insufficiency in such an instance. Preventive treatment, except for the recommendation to avoid emotional stress, remains a considerable problem since this patient is now essentially normotensive *despite the withdrawal of all antihypertensive drugs.*

The diagnosis and pathogenesis of such lesions of the cerebral circulation in hypertension will be discussed in another chapter (p. 133). In the arteriosclerotic hypertensive subject, two conditions often precede a cerebrovascular attack. These are preexisting cerebral arteriosclerosis and an abrupt rise in blood pressure. Perhaps in the elderly the increased arterial rigidity in some fashion compromises flow through the area of "spasm" or its collateral vessels, with a resulting tendency to thrombosis. Certainly this complication rarely occurs in a younger person with more normal cerebral arteries and an equal degree of acute blood pressure elevation. One may speculate that these acute rises in blood pressure engender a reflex cerebral vasoconstriction similar to that clearly visualized in the experiments of Byrom (1954) in which the cerebral vessels of rats were subjected to inspection during and after cure of renal hypertension. With the rise in blood pressure, focal constrictions of the cerebral arteries appeared followed by thrombosis and areas of cerebral softening. Reduction of pressure by removal of the clip on the renal artery

caused cerebral vasoconstriction to disappear, but permanent lesions remained where the process had reached the thrombotic stage.

If transient cerebral episodes occur frequently in the elderly patient during known acute rises in blood pressure, a vigorous effort should be made to prevent recurrence of the hypertensive crises. Clinical evidence that prolonged blood pressure reduction reduces the frequency of cerebral vascular accidents in younger patients (Pierson, 1957) makes it reasonable to adopt the same philosophy for the older individual. However, treatment is a difficult matter. If the blood pressure is not usually greatly elevated, it is hard to justify the use of any antihypertensive drugs, particularly since the acute hypertensive episodes that follow emotional stimuli cannot be prevented by any drug now available. Thus, a somewhat unsatisfactory compromise is necessary in the treatment of the arteriosclerotic form of hypertension in which acute serious cerebral attacks have occurred. The regimen includes a major effort to shield the patient from emotional stimuli, the liberal use of reserpine, salt restriction, and dehydrating drugs such as chlorothiazide If with such treatment the blood pressure does not fall to near normal levels, small doses of ganglion blocking drugs may be administered. Since these patients are often sensitive to such agents and exhibit erratic responses, care must be taken to keep the dose low enough to avoid syncopal episodes.

SUMMARY

Increases in cardiac output or arterial rigidity may produce considerable systolic hypertension. Increase in cardiac output is seen in thyrotoxicosis, aortic insufficiency, and heart block, but these conditions are rarely difficult to distinguish from essential hypertension. Increased arterial rigidity causes a predominantly systolic hypertension in many older patients and in younger individuals with a predisposition to arteriosclerosis. Because of the loss of elasticity, these patients may show an excessively labile blood pressure, but only mild forms of treatment are indicated. While the condition is generally considered benign, retinal lesions, aneurysms, and left heart failure may require more strict

control of the blood pressure. The frequency of cerebrovascular accidents during acute hypertensive episodes is emphasized. These individuals must be protected as far as possible from emotional stress, and in some instances may require close supervision and treatment with small doses of the more potent antihypertensive agents.



CHAPTER 7



Hypertension With Lesions of the Nervous System

INFLAMMATORY LESIONS OF THE BRAIN STEM

Of the existence of a mechanism within the central nervous system to raise and sustain the blood pressure at a high level there is little doubt. If direct observation of the effects of emotional stress and anxiety on the blood pressure of normal and hypertensive patients were not enough, this hypothesis would be supported by observations made in a comparatively rare group of individuals with central nervous system lesions.

Perhaps the most common disease in this group of patients is *bulbar poliomyelitis.* In this condition, as in other infections involving the brain stem, a clear-cut elevation in blood pressure is sometimes produced (Weinstein, 1951). The hypertension has certain unusual characteristics, such as associated tachycardia, a disproportionately high diastolic reading, extreme lability of the blood pressure, and remarkable sensitivity to the use of ganglion-blocking agents. Most striking is the lack of retinal vascular disease. Rarely does one observe focal retinal vasoconstriction, hemorrhages, or exudates. The heart is usually well compensated and one is amazed that a patient can withstand such high diastolic blood pressure levels for so long without signs of vascular deterioration By contrast similar degrees of blood pressure elevation associated with acute nephritis or toxemia of pregnancy are poorly tolerated.

INCREASED INTRACRANIAL PRESSURE

The hypertension associated with increased intracranial pressure, as in the case of a brain tumor, is recognized by the rapid onset of increased pulse pressure and slowed pulse rate. The increased spinal fluid pressure may cause papilledema, mental confusion, coma, or delirium as in the hypertensive encephalopathy associated with malignant hypertension (Palmer, 1948). However, the latter condition may usually be distinguished by marked retinal arterial vasoconstriction, albuminuria, and impaired renal function.

Central nervous system disturbances may superimpose an acute neurogenic hypertension on a previously mild hypertension. Two conspicuous examples of this situation have been seen in our clinic; no doubt other clinicians have had similar experiences.

The first example is typified by the patient who is first seen with the history and findings of *subarachnoid hemorrhage.* The blood pressure is very high. The borders of the optic disc are blurred; hemorrhages and exudates are seen; there is relatively little arterial constriction. It is presumed at first that this is a patient with malignant hypertension and hypertensive encephalopathy. If a lumbar puncture is performed and red blood cells are found in the spinal fluid, it is an indication that a subarachnoid hemorrhage has occurred. The blood pressure is reduced by vigorous treatment, and the patient survives. In the belief that the hemorrhage was the consequence of a severe elevation of the blood pressure, a vigorous antihypertensive program is instituted. As time passes, it is gradually realized that a spontaneous reduction in the blood pressure has occurred, and this is finally proved by the withdrawal of all drug therapy. The only reasonable sequence of events seems to be that during the hemorrhage a rise of intracranial pressure had occurred, which in turn produced acute but transient hypertension. Recognition of this sequence of events after subarachnoid hemorrhage is important for rational therapy.

The second example of acute neurogenic hypertension superimposed on mild hypertensive disease may be illustrated the following résumé of a specific case.

Case History

An obese middle-aged woman with moderate and long-standing hypertension was admitted to the hospital in coma, with a very high blood pressure and papilledema. The patient's relatives stated that her mental confusion had begun several days before and progressed until they had called a physician who had the patient admitted to the hospital. Vigorous antihypertensive therapy brought the blood pressure down, but the mental status did not improve. The relatives were questioned more closely and then it was learned that, some weeks before, the patient had experienced a moderately severe head injury after falling downstairs. A diagnosis of subdural hematoma was made, the clot was removed, and the patient recovered consciousness. The blood pressure returned to the level usual for her prior to the accident.

COMMENT. The importance of a history of head injury in distinguishing between subdural hematoma and hypertensive encephalopathy was obvious in this case.

Reduced activity may occur in the cerebral centers that elevate the blood pressure, particularly after some cerebral thrombotic episodes. This may result in an occasional "cure" of prolonged and severe hypertension (Griep, 1951). Likewise, the occasional onset of chronic postural hypotension following head injuries and the production of persisting orthostatic hypotension after administration of certain plasmoquin derivatives which affect the brain stem (Freis, 1947) indicate that a center in this area is responsible for maintaining a normal blood pressure or at least a normal postural reflex.

LESIONS OF AUTONOMIC CEREBROSPINAL INNERVATION

Perhaps the most dramatic form of neurogenic hypertension follows *spinal cord injury.* The reason for the headaches and convulsions following bladder lavage or bowel evacuation in victims of paraplegia was well explained by Thompson and Witham (1948), who demonstrated the acute pressor effect of increasing the pressure within the bladder or bowel in these patients. These

authors reported that the administration of ganglion-blocking agents in relatively small doses would readily prevent the acute hypertensive crisis. For significant hypertension to occur, the spinal lesion must damage the cerebrospinal pathway controlling autonomic activity above the upper thoracic region, so that the *autonomic spinal reflex arc thus released will include* the splanchnic efferent pathways. As with the motor reflexes, the *moderating influence of the central nervous system is important* in inhibiting the discharge of autonomic reflex arcs.

A rare form of hypertension that has been related to abnormal sympathetic nerve activity is that which is associated with *porphyria.* Hypertension commonly accompanies the crisis of this disease, appears to be due to lesions of the sympathetic nerves, and usually responds to ganglion-blocking agents.

SUMMARY

Occasionally, damage to the central nervous system will produce acute hypertension, especially in bulbar poliomyelitis and in conditions associated with increased intracranial pressure. Spontaneous "cure" of hypertension and postural hypotension may also follow injury to certain centers in the brain. Attention is also directed to the acute hypertensive crisis that may occur in porphyria and in paraplegic patients following visceral stimulation.



CHAPTER 8



Relationships Between Hypertension and Other Diseases

CONDITIONS IN WHICH AN ASSOCIATION WITH HYPERTENSION IS COMMON

POLYCYTHEMIA

A form of primary polycythemia is frequently described that is characterized by associated hypertension, the so-called Gaisboeck's polycythemia. This type is said to occur more frequently in middle life and to be less severe than the usual forms. Most authorities now believe that Gaisboeck's disease represents an association between the two conditions rather than a special variety of polycythemia, since the more usual form of polycythemia, in which there is a greater increase in blood viscosity, does not produce hypertension. The plethoric countenance of hypertensive patients sometimes brings to mind the appearance of polycythemia rubra vera. Many complications of this disease are also seen in hypertension, such as dizziness, headaches, mental confusion, and small thrombotic episodes. It is not unreasonable to assume that the effects of the two diseases occurring coincidentally might be additive. If the hematocrit and total red blood cell volume are substantially elevated in a case of severe hypertension, reduction of the blood volume by phlebotomy or P^{32}

administration may occasionally be justified. It is not to be expected that these measures will specifically lower the blood pressure, but they may provide relief from symptoms and possibly afford greater protection against cerebral thrombosis. That plethora may cause symptoms in the hypertensive patient is interestingly illustrated by the following case.

Case History

A 54-year-old man with hypertension of 10 years' duration was found to have a casual blood pressure of 202/128 mm. Hg and 190/118 mm. resting. The hematocrit was 56, the hemoglobin 18.5 Gm., and the white blood cell count 13,600. There was no other evidence of vascular involvement of target organs.

In the Hypertension Clinic the patient was given intravenously 50 mg. of the short-acting ganglion-blocking agent, Pendiomid, with an *immediate blood pressure reduction to 146/106 mm. Hg.* Spontaneously, he described relief from a feeling of mental con*fusion and fullness in the head. The symptoms returned the next* day as the blood pressure rose but was again relieved when in successive phlebotomies, 1,500 ml. of blood was removed. This procedure did not lower the arterial pressure but reduced the hematocrit to normal.

COMMENT. This man had one of the characteristic cerebral symptoms of hypertension. He also had a mild degree of polycythemia as measured by an increase in hematocrit. It was pos*sible to relieve his dizziness and mental clouding either by re*duction in blood pressure or in total red blood cell volume. It may be presumed that the improvement was in each instance the result of a reduction in cerebral blood volume: at first from the cerebral circulation to the venous pools in the abdomen, and after the phlebotomy, by reducing the total blood volume including that perfusing the brain. A similar relief from headache and the feeling of *"fullness" in the head is often seen following* the redistribution of blood after sympathectomy for hypertension. In this case removal of sympathetic visceral tone may allow redistribution of blood away from the cerebral region.

CONDITIONS IN WHICH AN ASSOCIATION WITH HYPERTENSION IS UNCOMMON

CIRRHOSIS OF THE LIVER

It has long been recognized that, statistically speaking, cirrhotic patients are less likely to have hypertension than those without cirrhosis Dr. Hubert Loyke (1955) has pointed out that the blood pressure of the hypertensive patient who develops cirrhosis falls to normal at about the time that a reduction in the albumin:globulin ratio appears. Since experimental renal hypertension requires for its development a protein formed in the liver (hypertensinogen), one may speculate that the cirrhotic liver fails to synthesize this particular protein.

While certain forms of acute hepatitis with jaundice are associated with a reduction in previously elevated blood pressure (Raaschou, 1954), not all forms of liver disease exhibit this phenomenon. In one instance, jaundice following administration of chlorpromazine did not affect the blood pressure.

ACUTE AND CHRONIC INFECTION

A dramatic alleviation of hypertension frequently accompanies certain forms of acute and chronic infection. This is particularly demonstrated when a patient with an elevated blood pressure contracts a urinary infection caused by a gram-negative organism. Even a mild "cold" or an attack of "influenza" may lower the blood pressure temporarily or reduce the daily requirement for antihypertensive drugs. This effect has been used therapeutically in the treatment of malignant hypertension with pyrogens (Page, 1951). Unfortunately, the blood pressure rises again after the toxic or febrile reaction has cleared.

RHEUMATOID ARTHRITIS

It has been claimed that there is a negative correlation between arthritis and hypertension (Turner, 1954). Since any toxic or debilitated state may reduce the blood pressure of the hypertensive patient to normal, one might speculate that the

inflammatory process in the joints had prevented the appearance of hypertension.

CANCER

Several reports have indicated that hypertension is rarely associated with cancer. In one study the factor of debility seemed well excluded (Moore, 1956).

SECTION III

PRIMARY HYPERTENSION



CHAPTER 9



Definition, Predisposition, and Natural History of Primary Hypertension

DEFINITION

Definition by Elimination of Other Causes of Hypertension

In the foregoing chapters the well-recognized causes of elevated blood pressure have been reviewed. Hypertension in these instances should be designated as secondary to the underlying pathologic condition. The disease about to be discussed is by contrast a primary or "essential" condition Only in that form of hypertension secondary to generalized arteriosclerosis is it sometimes impossible by appropriate clinical methods to make a clear-cut distinction from primary hypertension. Since the arteries lose their elasticity in long-standing essential hypertension as well as in the arteriosclerotic variety, an element of vascular rigidity finally enters into every case of primary hypertension and is the chief cause of the widened pulse pressure seen in essential hypertension.

Definition of Blood Pressure Elevation

It is now necessary to consider what are the accepted upper normal limits for the blood pressure. Since mortality rates increase gradually as the blood pressure of the normal person rises

from "subnormal" to "hypertensive" levels, as Pickering (1955) has emphasized, there is no point above which the level of the blood pressure can be related to a distinct increase in mortality rate. Therefore, if "disease" is meant to define an illness affecting life expectancy, no upper normal limit for blood pressure can be defined. To make the problem more difficult, the influence of aging on the blood pressure of the "normotensive" subject must be taken into account. The old statement that the upper normal level of systolic pressure should not exceed 100 plus the patient's age describes with fair accuracy the range of blood pressure observed in the United States population by Master and his collaborators (1950, 1952). Perhaps this systolic increment with age reflects the gradually increasing rigidity of the arteries. It may be that such progression is in itself a sign of the greater tendency of Western man to acquire arteriosclerosis with advancing years, since a similar increase in blood pressure with age is not reported in the Oriental or in the primitive African native (Donnison, 1929). If this view is correct, it would conform to the observation of Mann, Munoz, and Scrimshaw (1955) that the level of blood cholesterol also does not rise with age in primitive populations.

Despite these considerations, some admittedly arbitrary definition of abnormal blood pressure is needed, if only for the purposes of further discussion. It is, therefore, proposed that in a patient under the age of 50, hypertension is present when the systolic level exceeds 150 mm. Hg and the diastolic is in excess of 90 mm. Many authors have placed emphasis only on the diastolic blood pressure, and certainly this is the more important from the standpoint of the physiological load on the circulation. However, both levels are elevated in essential hypertension and contribute equally to the increased mortality rate, according to Actuarial Studies (1940). Since the magnitude of elevation of the systolic pressure is usually greater than the diastolic, it is more convenient to discuss essential hypertension in terms of systolic pressure elevations. For this reason, the discussion in this book will refer particularly to the systolic reading but will assume that there has been a commensurate elevation in the level of the diastolic pressure.

Having chosen an arbitrary upper limit for a normal reading a decision is now required as to whether the blood pressure must

always be above normal limits, often above these limits, or even occasionally above these levels, to constitute a pathologic condition. Here again a precise decision is difficult. Under appropriate conditions of emotional stress the blood pressure of any normal subject may exceed 150/90 mm. Hg. On the other hand, in truly hypertensive patients blood pressures usually above this level may frequently fall to normal even on brief hospitalization. A working compromise is therefore necessary. In the Hypertension Clinic, the term "essential hypertension" is not used until casual office blood pressures at several visits have all shown an elevation above 150 mm. Hg systolic and 90 mm. diastolic.

Primary Hypertension: A Characteristic or a Disease

The very obvious difficulty in segregating the early hypertensive patient from the normal one has led Pickering (1955) to propose an important and challenging concept: namely, that elevated blood pressure appears to represent not a disease but a graded characteristic of the individual, determined by inherited and environmental influences. He believes that just as there are tall and short individuals so there are different levels of blood pressure in the population. He maintains that in contrast to height, which has no apparent effects on longevity, elevated blood pressure increases mortality rate, since it accelerates the development of vascular disease and causes fatal vascular accidents. The principal evidence for his view is that a plot of the frequency distribution of blood pressures in the normal population shows no sharp break from the normal to the severely elevated or "disease" level These curves, however, do not follow a typical frequency distribution as, for example, if the height of individuals were plotted. There are more cases with blood pressures above than below the median. An alternate explanation of his findings might be that there is in fact a normal frequency distribution for blood pressure in the population on which is superimposed the curve for individuals with varying severity of hypertensive disease. Nevertheless, the challenging hypothesis of Dr. Pickering does explain why it is so difficult to differentiate the normal from the abnormal blood pressure. It conforms with the experience that blood pressure elevation in itself is an im-

portant determinant of vascular disease and disability, and if it is accepted with the implicit challenge to distinguish between those cases of hypertension that are simply an inherited or acquired characteristic and those due to as yet unknown morbid processes, the hypothesis will have served a very useful purpose in advancing our understanding of hypertension and hypertensive disease in general.

PREDISPOSING FACTORS

Labile Blood Pressure

Patients who show only random readings above "normal" limits are considered to have "labile blood pressure," a description that should carry no adverse connotation concerning prognosis, employment, or insurance eligibility. In a business world increasingly dominated by disability retirement plans, to classify a young person with labile blood pressure as having "essential hypertension" is to make a grave decision with respect to his future health records, to frighten him unnecessarily in many instances, and to imply to the physician or employer a prognosis not necessarily justified. Unfortunately, the survival rate of patients with "labile blood pressure" as defined above has not been established but three studies bearing on this point indicate a generally favorable prognosis. Levy *et al.* (1947) studied the long-term prognosis of Army officers who had transient elevations of blood pressure on initial examination for entrance into the Army but whose readings fell to normal on a second examination shortly thereafter. The death rate from all cardiovascular causes in the ensuing 35 years was compared with that of a similar number of individuals accepted at the same time who did not show transient elevations of blood pressure. Six per cent of the group who had originally had labile blood pressures died of cardiovascular disease of all kinds while 3 per cent of the group with initially normal blood pressure were deceased for similar reasons.

In another study Hines (1950) measured the frequency of later hypertension in normotensive individuals who showed an abnormal rise in blood pressure after immersion of the hands in

ice water. Fifteen years later 54 per cent of these "labile hypertensive" subjects exhibited a diastolic blood pressure in excess of 100 mm. Hg, while this level was exceeded in 19 per cent of subjects with a normal reaction to the test. To express these statistics somewhat differently: after the lapse of considerable time, one half of a group of subjects with labile blood pressure became hypertensive. Presumably the other half remained free from hypertensive complications, since by the time of the follow-up study most of them must have reached middle life or beyond without a sustained blood pressure elevation. Experience shows that there is little likelihood of the subsequent development of a serious disease with vascular complications after this age. Furthermore, it is probable that many of the group who did develop hypertension exhibited only a minor degree of blood pressure elevation, and therefore were also not subject to the risk of serious vascular disease. It may be concluded from this study that hyperreactivity of the blood pressure, while occasionally premonitory of hypertension, is clearly no reason for a serious prognosis.

A third report concerns the course of two groups of patients who on admission to a Viennese hospital were found on random examination to have either a normal or a moderately elevated blood pressure reading (Doujak, 1957). In follow-up studies 16 years later both groups showed a high and approximately equal frequency of hypertension (defined as blood pressure exceeding 140/90 mm. Hg). Unfortunately, the validity of the data is compromised by the fact that only 30 per cent of the originally selected cases could be contacted for later examination.

One may summarize by stating that there is little doubt that persons with labile hypertension are more likely to acquire hypertension in later years, but the risk is so slightly increased as to make it unjustifiable to label all cases of occasional or transient elevation of blood pressure as examples of essential hypertension.

Familial Influences

Many studies have shown the importance of familial factors in predisposing to hypertension. Individuals who develop the disease usually have hypertensive parents. Platt (1947) has come to the conclusion, from a careful study of the blood pressure of

patients and their first degree relatives, that the disease is inherited as a dominant characteristic. Hines (1940) has stated that when both parents have hypertension, the frequency of the disease in the children rises to 90 per cent. His studies in identical twins, moreover, have shown the high frequency of coexistence of the disease (1957). Finally, Ayman (1934) has demonstrated that the blood pressure of sons and daughters of parents with hypertension is higher than that of the offspring of nonhypertensive patients. Thus, there is little doubt that the hypertensive trait is inherited or is acquired in early life from the *familial environment.*

Racial Influences

A racial or geographic predisposition to hypertension has also been described. While it is rarely observed in the American Indian population (Cohen, 1953), the American and West Indian Negro is frequently affected by the disease (Comstock, 1957; Saunders, 1942). Malignant hypertension and cerebral failure are common in these populations, which conforms with Pickering's thesis that the complications of the disease are related to the duration and severity of blood pressure elevation. The racial predisposition in West Indian Negroes is very striking. In the Bahamas, Moser (1958) found a frequency of blood pressure exceeding 150/100 mm. Hg to be present in 20 per cent of Negro males and females aged 30 to 34. On the island of Curaçao, 10 per cent of school children less than 18 years old showed elevations of systolic blood pressure exceeding 140 mm. Hg (Spitzer, 1949). That this remarakable frequency of hypertension in the West Indian Negro may have an environmental rather than a genetic basis is suggested by the relatively normal values reported for the West African Negro (Williams, 1941). However, in the latter group a high incidence of chronic disease and malnutrition, conditions known to lower the blood pressure in *hypertension, may be responsible for the difference between the* two populations.

Influence of Sex

A sex difference in the incidence and severity of hypertension has also appeared in all careful studies so far. The illness occurs

more frequently in the female, at a ratio of approximately 3:2, but the mortality rate is higher in the male, perhaps owing to his greater vulnerability to arteriosclerosis. Cerebrovascular deaths occur about equally in the two sexes (Pierson, 1957), but death from coronary thrombosis is undoubtedly more frequent among male patients.

NATURAL HISTORY

It is very helpful to consider essential hypertension in terms of its total life history. Perhaps inborn in the infant, first expressed as a slightly abnormal blood pressure in youth, later manifested as a consistent elevation in middle life, this disease finally is recognized by the patient as symptoms and signs of target organ failure develop in his mature years. The final stage is death from a cardiac, cerebral, or renal cause occurring ten to twenty years earlier than the similar vascular accidents that frequently terminate the life of the normotensive subject in later years. The vascular disease to which we are all heir comes in hypertension more swiftly; and tragedy strikes in the mature, not in the declining years.

The average course of the disease is thus described. Yet, in some patients, particularly the young ones with malignant hypertension, these tragic events are compressed into a few short years while in many others the disease appears to be arrested in one of its various preliminary stages, the vessels withstanding the increased strain without shortening the patient's life span. One fact is reasonably certain: once the disease has become established, the blood pressure rarely reverts to normal. The disease, however, may cease to progress beyond a certain point. A labile blood pressure may always remain thus or, after the blood pressure has climbed to a certain moderate plateau, it may never provoke a vascular lesion. However, when it is very high or a vascular complication is already noted, death from hypertension is the rule. Some individuals with severely elevated blood pressure for many years pursue a benign course and thus constitute an apparent exception to this rule. Remembering such exceptions, many physicians refuse to take seriously the importance of treating cases of severe hypertension—especially

patients and their first degree relatives, that the disease is inherited as a dominant characteristic. Hines (1940) has stated that when both parents have hypertension, the frequency of the disease in the children rises to 90 per cent. His studies in identical twins, moreover, have shown the high frequency of coexistence of the disease (1957). Finally, Ayman (1934) has demonstrated that the blood pressure of sons and daughters of parents with hypertension is higher than that of the offspring of nonhypertensive patients. Thus, there is little doubt that the hypertensive trait is inherited or is acquired in early life from the familial environment.

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TABLE 6. PROGNOSIS IN HYPERTENSION WITH PARTICULAR REFERENCE TO CEREBROVASCULAR MORTALITY

			Initial status		*Follow-up*		
			Minimum B. P.	*Age range*	*Duration*	*Mortality*	
Published report	*Year*	*No. cases*	*Syst./dias. mm Hg*	*Years*	*Years*	*Total (per cent)*	*CVA* (per cent)*
Rice	1933	327	160/90	Av 56	5–10	9	2
Paullin	1926	76	160/—	30–75	5–17	26	9
O'Hare & Holden	1952	100	Unknown	Unknown	10–34	29	14
Bechgaard	1946	1038	160/100	40–69	4–11	29	14
Frant *et al.*	1950	418	150/100	Unknown	8–9	31	2
Leishman	1953	151	—/100	Under 50	2 5–5	34	11
Rosling	1934	279	160/—	Unknown	8	39	6
Rasmussen & Boe	1945	100	160/95	30–85	6	52	19
Griep *et al.*	1951	117	—/110	Under 50	8–10	54	22
King *et al.*	1942	794	175/100	Av. 40	10–16	73	8
Bechgaard	1946	69†	160/—	Unknown	8	64	38
Pierson & Hoobler	1958	71†	—/110	30–50	10–12	70	45

* CVA: frequency of death from stroke

† Cases selected for inclusion in study because of a prior history of a cerebrovascular episode.

in Ap-
71 Pa-

set of the blood pressure elevation was not known. The presence of a vascular complication very considerably worsened the prognosis. Once a blood pressure level exceeding 200/110 mm. Hg was established it did not change greatly over the years of follow-up. Further elevation did not precede the development of the fatal complication in most instances. It seemed as if the blood pressure, having reached a certain plateau, was no longer a determinant of outcome. From this point on, the factor of vascular vulnerability played the major role. Patients with diastolic blood pressures in the range of 120–129 mm. Hg at the start of the study were separated into two groups: those with and those without manifest signs of target organ disease. In the group without such complications, 12 of 14 survived for 10 years, whereas 11 of 13 in

the group with these complications died during the same interval (Table 7).

From what has been said one might infer that blood pressure itself is of little or no importance in determining prognosis. That this is not true can be learned by further inspection of Table 7,

TABLE 7. EFFECT OF INITIAL BLOOD PRESSURE AND OF CARDIAC OR CEREBROVASCULAR COMPLICATIONS ON PROGNOSIS IN HYPERTENSION

Initial diastolic blood pressure mm. Hg	*Complications at initial examination**			
	Present		*Absent*	
	No. living	*No dead*	*No. living*	*No. dead*
110–119	3	2	17	5
120–129	2	11	12	2
130–139	3	9	6	5
140–170	3	17	4	2
Total	*11*	*39*	*39*	*14*

* Complications included prior cerebrovascular accident (6 cases), persistent albuminuria, electrocardiographic abnormalities, or heart size increased by more than 15 per cent of normal

Nine patients died of nonhypertensive or unknown causes during the 8- to 10-year observation period Consecutive patients were selected who had been referred to the University Hospital, whose initial diastolic blood pressure on at least two outpatient examinations exceeded 110 mm Hg, who completed the prescribed preliminary examinations, and who underwent no treatment in the subsequent interval other than usual sedative or low salt diets None was over the age of 50. None had obviously terminal complications, azotemia, or papilledema at the time of inclusion in the study

Reprinted from Griep, A. H., Barry, G. R, Hall, W C, and Hoobler, S. W: The Prognosis in Arterial Hypertension. Report on 117 Patients under 53 Years of Age Followed 8 to 10 Years *Am J M Sc* *221*, 239, 1951.

where it is shown that even in the absence of vascular complications 23 per cent of patients with a diastolic blood pressure in the range of 110–119 mm. Hg had died in contrast to 41 per cent whose initial diastolic readings were in excess of 130 mm. Hg.

Because of varying degrees of individual vascular vulnerability to hypertension, the relationship between blood pressure and ultimate mortality rate is not precise. One may further speculate that the blood pressure in the clinic is not always representative of the "usual" blood pressure. Two patients with the same clinic recordings may have different readings in the home. It is possible that the patients in the study with a high blood pressure in the clinic and a good survival rate maintained lower readings when away from the clinic than the group with the worse outcome.

This factor must also be assessed when considering the relationship between blood pressure levels and mortality rate from hypertension.

The presence of vascular complications was possibly related to the duration of elevated blood pressure, an unknown factor in Griep's study. To support this view many of the survivors who initially had shown no complications, were found on follow-up 10 years later to have acquired signs of vascular disease Perera (1955a) has approached the problem of prognosis by selecting cases on the basis of an actual record of the date of onset of hypertension together with records of continuous observation of the course of the disease until death. From this information he has made the following generalizations concerning the average life history of the hypertensive patient: initial elevations of the blood pressure are usually encountered before the age of 45; a period of labile hypertension with gradual transition into consistently elevated casual readings in the clinic occurs during the first 5 to 10 years. In the next 5-year interval the blood pressure remains more or less at the same level and the patient gradually becomes aware of his disease because of symptoms or complications of minor nature. In the last 5 years, at a variable rate of occurrence, serious complications and a fatal outcome ensue. The average age at death in Perera's series was 52 years. Some patients, however, were still living 40 years after the onset of the elevated blood pressure. Only a small proportion had died of causes unrelated to hypertension. The median duration of disease from onset of the established phase to death was 9 years

Some authors have introduced the concept of vascular disease as distinct from hypertension and have implied that there is no advantage to be gained by lowering the blood pressure, since the outcome depends only on the "vascular disease." In this discussion no attempt has been made to deny the difference in vascular vulnerability of two patients with the same blood pressure readings. However, to deny that blood pressure has an important influence on prognosis is to ignore clinical experience and to refuse the only possible approach to the treatment of hypertensive disease. While not accepting the elevation of the blood pressure as the sole determinant of prognosis, one must still hold to the truth that the higher the pressure, the worse the prognosis. Were

it possible to know the duration and daily fluctuations of the blood pressure, it is probable that an even closer correlation would be found between blood pressure, vascular damage, and death.

It will, therefore, be seen that despite fragmentary and inadequate studies concerning the natural history of hypertensive disease, the few carefully planned studies that have been reported are in essential agreement. They indicate that after the blood pressure has reached a certain point, final death from a vascular complication is almost inevitable. The major determinants of survival are the duration and height of the blood pressure, which is a reasonably measurable item, and the vascular vulnerability of the particular patient, a characteristic that is hard to define but can be determined by the detection of a vascular lesion upon careful examination of the circulatory system. When such a defect is noted in the patient with hypertension, the prognosis is grave and efforts to reduce the blood pressure should be intensified. In the chapters that follow the defects will be identified, and the prognosis of the individual patient will be classified in terms of his blood pressure and vascular vulnerability together with his background of age, sex, and race.

SUMMARY

Essential hypertension is identified by the absence of any apparent cause and by virtue of a usual blood pressure level above 150/90 mm. Hg on repeated casual determinations in a subject under the age of 50. Arteriosclerotic changes in the larger vessels further elevate systolic blood pressure approximately one millimeter per year of age, and also contribute to the widened pulse pressure and elevated systolic level in essential hypertension. This definition of "essential hypertension" is an arbitrary one, since there is no clear break in frequency distribution or in mortality rate between individuals with "normal" and "elevated" blood pressure as defined above.

Many young subjects display a "labile blood pressure," which implies a slight increase in the tendency to develop essential hypertension in later years. Certain familial and racial influences also predispose to hypertension.

The average course of the disease consists of a 5-year period of labile hypertension, 5 years of an established elevation of blood pressure usually without symptoms or complications, then a terminal 5- to 10-year interval in which vascular lesions develop in critical sites and death ensues from some complication of the disease. The height and duration of elevation of the blood pressure and the rate of development of vascular complications are the principal factors in determining the prognosis.

CHAPTER 10

Prognostic Evaluation of the Hypertensive Patient

THE BLOOD PRESSURE AS A GUIDE TO PROGNOSIS

The magnitude and consistency of the elevation in blood pressure are important factors in estimating the risk of hypertensive disease in an individual patient. A true evaluation of these influences is difficult to achieve from casual readings of the blood pressure taken at one or two office visits. Nevertheless, the prognosis and therefore the treatment depend on an accurate knowledge of these variables as well as on evidence of recent increases in the levels of the blood pressure. For this reason, the physician must obtain as many readings as possible, both from past records and during the initial period of observation, before he attempts to determine the prognosis. Sometimes it is of added help to instruct the patient in the technique of taking his own readings so that a record of the blood pressure levels during ordinary daily activity may be compared with office records. From this accumulated information one may obtain an estimate of the "usual" blood pressure and its variability. On the basis of this knowledge it will then be possible to classify the patient in one of the categories described below and to make a more accurate assessment of the contribution of the blood pressure to the individual's prognosis. Thus the initial blood pressure recorded for the patient with hypertension should be only one of a series of readings

collected for the purpose of determining the "average" or usual blood pressure.

In addition to securing from the patient or previous records a number of blood pressure readings, the physician himself should *obtain several readings before instituting* any antihypertensive treatment. The recumbent blood pressure after 30 minutes' rest should be taken at least once, since this procedure provides further information concerning the lability of the blood pressure and the effect of the office environment on it. Readings taken by the office nurse are more likely to represent the patient's usual blood pressure. A series of casual determinations may be obtained by requesting the patient to visit the office at frequent intervals during the preliminary studies necessary to exclude secondary hypertension. If the records so obtained are widely variable or inconsistent with the patient's apparent good *health, it may be well to lend him a blood pressure cuff* and have him take a series of home readings for the purpose of obtaining more accurate information concerning his usual blood pressure The following experience illustrates the value of this procedure in an individual case.

Case History

A 50-year-old woman was referred to the Hypertension Clinic because of a marked elevation of the blood pressure during the previous year. Despite many kinds of treatment, her physician *recorded blood pressure readings consistently in the range of* 250 mm. Hg systolic and 120 mm. diastolic. Although there was a history of hypertension in her family, she had never experienced any symptoms related to the disease. Moderate retinal arteriosclerosis and a casual blood pressure of 210/114 mm. Hg and 190/110 mm. after 30 minutes' rest were the only abnormalities noted during the physical examination. Urinalysis, intravenous pyelograms, Regitine test, and electrocardiogram were normal. The phenolsulfonphthalein excretion in 15 minutes was within the normal range. The initial impression was that the patient had moderately severe established hypertension without complications, but it was surprising that so few vascular lesions were found with this degree of apparently sustained blood pres-

sure elevation. The patient was accordingly instructed in the technique of recording her own blood pressure and a cuff was given to her. One month later she returned with a record of twice daily recumbent blood pressure readings in the range of 150/96 mm. Hg to 182/110 mm. It was concluded that at this age in life such blood pressures constituted a minimum threat to her health. A conscientious trial of rauwolfia alkaloids and salt restriction was recommended, but it was stressed that if the side effects were too unpleasant, all treatment might be discontinued with safety provided her disease showed no signs of progression on semiannual check-up.

COMMENT. On every office visit for a number of months marked elevation of the blood pressure had been recorded. These high casual readings had also been confirmed in the Hypertension Clinic. But the general physical examination, laboratory findings, and the retinal picture indicated no evidence of serious vascular disease. Because of this discrepancy, readings were obtained in the home. They showed a usual blood pressure in the mild labile range. This finding satisfactorily explained the absence of vascular disease and was of great reassurance to the patient and her referring physician.

This case provides one example of the usefulness of blood pressure determination in the home in supervising patients with hypertension. Certainly a much clearer picture can be obtained of the true blood pressure level than if one relies on the casual office reading or measurements made in the hospital. In patients with minimal elevation of the blood pressure, a record of the home readings is not essential since the prognosis is good and vigorous treatment is unnecessary. On the contrary, in patients with severe elevation of the casual blood pressure the decision concerning treatment may require more accurate knowledge of the usual level of the blood pressure. In the case cited above, for example, frequent blood pressure readings in the home permitted the physician to arrive at the important decision not to undertake a vigorous treatment program.

The blood pressure taken by the physician at the time of the first examination in the office or clinic will probably be the highest he will ever record; readings on subsequent visits will usu-

ally be substantially lower. Often treatment is started before this period has passed, and many reports of the apparent effectiveness of various treatment regimens are based on an inadequate initial period of observation. The evaluation of the blood pressure in the hospital is even more difficult For reasons that are not entirely clear, almost every patient at admission will have high readings that fall spontaneously in the next several days. This common experience also explains many overoptimistic reports concerning the effectiveness of various procedures for the treatment of hypertension. It is difficult to decide which measurement is truly representative of the usual daily blood pressure in the home. This probably lies midway between the lowest hospitalized blood pressure and the casual reading in the physician's office. Thus, while no certainty can be attached to any single observation, an average value for the patient can be estimated by multiple readings in office, hospital, and home. Such an evaluation of the blood pressure before treatment is of great importance, since a decision concerning prognosis depends upon knowing with some accuracy the patient's usual blood pressure.

Having reached an estimate of the degree of elevation and of its variability, one may then construct a useful classification. If the average casual readings vary between normal values and 180 to 200 mm. Hg systolic, the hypertension may be identified as *mild labile.* If these readings range from near normal (160–180 mm. Hg) to values well above 200 mm. systolic, the patient may be classified in the *extreme labile* category. Sometimes the blood pressure varies little but remains consistently below 200 mm. Hg. A patient with such readings would be classified as having *mild established hypertension;* while if the usual readings were consistently above 200 mm. Hg systolic and 110 mm diastolic, he would fall in a group labeled *moderately severe, established hypertension.* When pressures continuously above 240/130 mm. Hg are obtained, he would be considered to have *severe established hypertension.* The blood pressure classification outlined above will be used in the following pages of this book to describe the status of the individual patient.

In all cases the time factor should also be evaluated. If the casual blood pressure readings are substantially above those recorded one or two years before, hypertension can be considered

progressive, and a worse prognosis is indicated. On the other hand, if the blood pressure for many years has been approximately the same, one *knows the condition may be considered stationary* so far as the blood pressure is concerned, and attention must then be directed to the rate of development of the vascular complications of the disease.

EVALUATION OF HYPERTENSIVE VASCULAR COMPLICATIONS

Having estimated the height and stability of the blood pressure elevation and determined whether the condition is progressive, the physician should then form an estimate of the degree of vascular involvement resulting from the hypertension. In the preceding chapter emphasis was placed on the importance of vascular lesions in determining "vascular vulnerability" to hypertension in the prognosis of the individual patient. In the present section these signs of vascular disease will be more completely identified. They are summarized in Appendix 4, p. 264.

The objective signs of vascular disease center chiefly about four target organs; information concerning impairment of their function is summarized below.

RETINAL CHANGES

A serious symptom of vascular disease is sudden loss of vision; *this usually follows retinal thrombosis.* Retinal hemorrhages or exudates may give rise to scotomata or blurred vision. Consequently, the occurrence of impaired vision in the hypertensive patient is of major importance, and, were it not for the great ease and accuracy of an adequate ophthalmoscopic examination, *might well be the most important method of identifying the onset of a serious retinal vascular complication.* At every visit one should inquire concerning visual symptoms, since the occurrence of transient retinal exudates may otherwise be missed.

Four indices of the vascular status should be recorded *independently in the ophthalmoscopic examination:*

1. *Retinal arteriosclerosis.* This is measured by the frequency and severity of increase in arterial light reflex, displacement or

obstruction at arteriovenous crossings, and tortuosity of retinal arteries.

2. *Generalized or focal arteriolar constriction.* The frequency of sharp caliber reduction in the major retinal branches as well as in their fine terminations should be described carefully. Diffuse arteriolar constriction of a major degree is occasionally observed in the absence of focal areas of vascular narrowing but is more difficult to recognize with certainty.

3. *Hemorrhages or exudates.* Their character and approximate age is particularly important, for fresh hemorrhages or exudates that are soft and fluffy indicate recently progressive disease, while those lesions that are fading or are hard and well demarcated may suggest a past process that presents less of an immediate threat to the patient's survival

4. *Papilledema.* Sometimes it is difficult to be certain of this finding When it is present the disc margin is blurred in all points of its circumference and there may be a definite elevation of the vessels as they pass over the optic disc. The process may be more advanced in one of the two eyes With some experience it will be possible to tell early haziness of the disc margin before manifest papilledema develops. This usually occurs in the nasal region but is likely to be confused by the inexperienced person with the slight blurring of the nasal margin of the disc that may be seen normally.

The various grades of retinal arteriosclerosis have uncertain value in terms of predicting the extent of vascular disease. They do, [illegible] Retinal artery cor[illegible] ten[illegible]s treatment to lower the blood pressure These lesions develop rapidly in toxemia of pregnancy and in acute nephritis, they may disappear completely after these conditions subside. When they have existed for a considerable period of time in primary or secondary hypertension, they are not as easily reversible. For this reason it is preferable to avoid the term "spasm" in favor of the less specific term "focal vasoconstriction" Patients whose blood pressure has returned to nearly normal levels after sympathectomy have shown little or no improvement in the focal

arterial constrictions. Since the lesions may not improve with blood pressure reduction, they are not a guide to the effectiveness of antihypertensive therapy. The fact that they are usually irreversible is of importance also because it may explain why some few patients who show marked retinal artery vasoconstriction may otherwise exhibit a relatively benign form of the disease. At some previous time, such subjects may have experienced a serious exacerbation of the hypertensive process that has subsided, leaving only this trace in the retinal vasculature.

The presence of hemorrhages and exudates should be viewed with the utmost gravity. These lesions, particularly when fresh, indicate in most cases a "premalignant" stage of hypertensive disease and suggest a serious prognosis. Their presence may serve to predict a downhill course in a patient with established hypertension before it is indicated by other signs.

A distinction should be made between the hard exudate that follows previous retinal vascular disease and the soft or cotton-wool exudate that usually indicates an event transpiring in the preceding several months. Since exudates may come and go spontaneously, their disappearance does not necessarily guarantee that the hypertensive process has been brought under control. However, should a patient under treatment develop fresh exudates between one visit and the next, it may be inferred that his blood pressure control is not adequate and that more effective measures should be instituted.

Papilledema is, of course, the sign of very grave retinal vascular disease and requires treatment on an emergency basis if the patient is to survive. Blood pressure reduction to normal levels for several months may be required for papilledema to subside and even then a blurred disc margin may remain. This retinal picture may suggest to the physician who sees the patient for the first time that active malignant disease is present. Only follow-up observation and the clinical status of the patient may serve to differentiate such a "burned-out" process from the active disease.

Retinal vascular accidents are in a category by themselves. Insufficient evidence is available to indicate their over-all prognostic importance for the hypertensive patient. Thrombotic lesions of the central retinal artery or vein or their tributaries in-

dicate generally a serious prognosis. Since the lesions also occur in conditions unassociated with hypertension or in hypertension with relatively low blood pressure levels, it is not certain whether reduction of the blood pressure will postpone their recurrence. In the case history cited on p. 53 there appeared to be some improvement when the blood pressure was brought under control.

CARDIAC CHANGES

The severity and duration of the hypertensive vascular overload may well be estimated from its effects on the heart. This organ is usually affected in one of two ways: either by the development of left ventricular hypertrophy and dilation leading to frank congestive heart failure, or by the appearance of angina pectoris or coronary thrombosis.

The first sign of cardiac involvement, after substantial hypertension of more than several years' duration, usually consists of electrocardiographic abnormalities, especially T wave inversion or RS-T segment depression. These in themselves are not of serious import, but with the progressive development of tall R waves over the left precordium, and left axis deviation in the limb leads, the cumulative effect of work overload is evident. Finally, the electrocardiogram may display left bundle branch block. These latter findings should warn that the blood pressure has been too high or too long sustained, and that the hypertensive patient is entering a stage of his disease that can no longer be viewed complacently. Often these electrocardiographic findings are apparent well before symptoms of cardiac insufficiency.

In the course of the development of left ventricular hypertrophy, certain abnormal findings will appear on physical examination At about the time that cardiac hypertrophy is suggested by the electrocardiogram, one may be able to notice the increased diffuseness and force of the apical beat as the hypertrophied musculature of the left ventricle thrusts itself against the chest wall. Percussion at this time may reveal slight lateral and downward displacement of the left border of cardiac dullness. Upon auscultation, no distinctive abnormality indicative of this stage of the cardiac response to hypertension will be noted, although some decrease in intensity of the first sound at the

cardiac apex or the appearance of a presystolic extra sound is sometimes observed. The heart remains compensated, left ventricular emptying continues to be complete, and the heart delivers all the blood received from the left atrium. The history at this stage often is not informative. Occasionally, with heavy work, there is more than the usual dyspnea. The patient may sense the increased strength of the apical beat but he has usually become so gradually accustomed to this change as not to recognize it as abnormal. Circulation time and vital capacity are unchanged. Teleoroentgenograms may or may not show evidence of thickening of the left ventricular wall, recognized by a prominence in the left lower salient of the cardiac shadow. Only minimal enlargement can be detected. The compensated but hypertrophied heart shows signs of work overload but has not failed. As yet, there are no symptoms; consequently, this stage often goes unheeded and untreated.

The course of events now accelerates. On unpredictable occasions, usually during sleep or after vigorous exercise, small breaks in compensation occur. These are characterized by brief periods of dyspnea and breathlessness, particularly on exertion. They cannot certainly be ascribed to left ventricular failure since they might occur in normal persons in middle life after such activity. But then the patient reports that he awakes at night unable to catch his breath, or he requires two to three pillows for comfort. He sits at his bedside or goes to the window for air. The attack passes quickly and might go unmentioned except for careful questioning. At this point the need for treatment is urgent if further and more disastrous episodes are to be prevented. During such an attack, or perhaps in the interval, a new clinical sign is recognized: the development of a rapid heart rate with gallop rhythm. This indicates that the left ventricle is not getting rid of the load of blood delivered to it by the atrium Consequently, atrial pressure remains high during ventricular systole. When the mitral valve opens, the impounded blood rushes through the valve, striking the ventricular wall and producing the ominous protodiastolic extra sound of the gallop rhythm.

Signs of the disease now rapidly accumulate. Percussion and x-ray clearly show the heart to be dilated. Rales are audible at the right lung base on occasions. Dyspnea appears on lesser ex-

ertion and the patient needs more pillows at night Circulation time is prolonged. A systolic murmur appears, indicating relative tricuspid or mitral insufficiency. Edema, liver engorgement, and elevated venous pressure are observed. The original state of left ventricular decompensation has become generalized congestive heart failure. At this stage of decompensation in a case of severe hypertension, when the cardiac shadow by x-ray has clearly increased in size, only a few patients before the era of antihypertensive drugs were able to survive for more than two years (Griep, 1951).

In summary, cardiac failure that results from the overload of an established hypertension pursues a reasonably predictable course. A careful history, physical examination, and intelligent use of the chest x-ray and electrocardiogram will enable the clinician to detect the cardiac complication well before there is risk to life. The rapidity of the progression of the lesion can be determined by repeated examination. Minor electrocardiographic changes are not of great importance, but signs of left ventricular hypertrophy by electrocardiogram or physical examination are serious complications that demand attention. When cardiac dilation, congestive failure, or gallop rhythm becomes prominent, the complication is grave and treatment urgently required.

The cardiac vascular lesion secondary to hypertension may develop *in the direction of coronary sclerosis and terminate in* coronary thrombosis. Early recognition of this condition is more difficult but may be attained through careful analysis of the case history. In many patients with severe elevation of the blood pressure, particularly women, an atypical anginal syndrome develops that may be described as "hypertensive precordial pain." While there is a fairly characteristic substernal pain radiating to the left arm, other features of the syndrome do not resemble the classical description of angina pectoris Emotion and anxiety but not severe activity may bring on the pain and rest or nitro*glycerin may not relieve it. The sharp shooting pains that may* occur over the precordial region in this syndrome are relieved by effective reduction of the blood pressure and do not return while the blood pressure is under control. Coronary thrombosis rarely ensues. One is tempted to make the diagnosis of angina pectoris except for the notably atypical features. In some re-

spects the history suggests a form of cardiac neurosis sometimes seen in nonhypertensive women. Yet, how can one explain the improvement when the blood pressure is lowered even when the patient is not aware of this reduction? By analogy to a comparable syndrome in severe mitral stenosis, the term "hypertensive precordial pain" is proposed to describe this symptom. Perhaps the left ventricle, acutely distended by a rise in systemic pressure, is called upon for increased work while coronary flow is impeded by high intraventricular pressures. This would be analogous to the presumed origin of pulmonary hypertensive pain in mitral stenosis.

True angina pectoris also occurs as a serious manifestation of hypertensive vascular disease. As in patients without hypertension, coronary thrombosis may follow angina, but frequently infarction occurs unexpectedly. This vascular accident of hypertension does not seem reasonably predictable unless typical angina pectoris or a previous coronary thrombosis give warning. The appearance of angina pectoris serves notice that the hypertensive patient has entered into a serious complication of his disease and it is not unreasonable thereafter to expect a median survival of about 5 years. In contrast to the situation in hypertensive heart failure, reduction of the blood pressure is less likely to affect the prognosis of hypertension complicated by coronary artery disease.

Cerebrovascular Changes

Death from hypertensive cerebrovascular disease is the most feared and most unpredictable of all accidents. The frequency of this complication is variously reported (see p. 77); in our experience it ranks equally with cardiac death as a terminal event (Griep, 1951). In the cerebral circulation, early signs of vascular disease are not easily identified and a "stroke" may come without warning. The only premonition may be a transient focal neurologic disturbance or a severe attack of confusion or dizziness. Such an episode indicates that the hypertensive patient has ...ched a serious stage in his disease. If a stroke is to be pre...ted, action must be taken promptly. The importance of the ... cerebral episode in determining the prognosis in hyper... ... by the ... report of Pierson (1957) the ...

based on experience at the University of Michigan Hospital. In reviewing the records of several thousand hypertensive patients seen 10 years previously in the University Hospital 71 patients under the age of 60 who had had well-defined focal neurologic disturbances were selected for follow-up. Thirty per cent experienced fatal cerebrovascular recurrences, mostly within 5 years after the first attack. Almost as many died of cardiac failure or coronary thrombosis, although these features were often not apparent on the initial examination. The fact that so many patients died of other complications of hypertensive vascular disease emphasizes still further the thesis that vascular involvement in hypertension is a general process, and that when the first vascular lesion appears clinically, many others may be in the formative state in other target organs. The relation between hypertension and the cerebrovascular mortality rate was demonstrated by the finding that significant blood pressure reduction following sympathectomy reduced the cerebrovascular death rate from 30 per cent to 5 per cent. This study further emphasized the importance of careful history-taking as the only method of accurately identifying cerebrovascular disease. All types of focal disturbances from the most mild and transient episode to a sustained hemiparesis appeared to worsen the prognosis to an equal extent.

It must be admitted that cerebral hemorrhage may strike without any warning, particularly in the patient with a marked elevation of the blood pressure. The report of Taylor and Page (1945) would suggest that in fatal cerebral hemorrhage some premonitory features such as severe nuchal headaches, retinal hemorrhages, or marked hypertension usually preceded the fatal attack. At lower blood pressure levels, serious cerebral accidents are usually preceded by a transient neurologic disturbance, but if the blood pressure consistently remains in the range of severe established hypertension, the absence of cerebral symptoms or of other signs of vascular disease is no guarantee that apoplexy may not occur.

Renal Changes

In some cases, particularly those with very high blood pressure, small amounts of albuminuria are observed. This finding is related to the hypertension, since reduction of the pressure

will frequently result in disappearance of proteinuria. It may be presumed that the hypertension in some way increases the excretory rate for albumin beyond the ability of the tubules to reabsorb it. Marked and continuous albuminuria in the patient with hypertension usually carries one of two connotations: either the proteinuria is secondary to unrecognized primary renal disease or the renal vascular bed is excessively vulnerable to the hypertension In either instance the prognosis is not good. In such a case the phenolsulfonphthalein excretion, the urea clearance, or the urine concentrating power will be moderately impaired. This type of patient, who exhibits marked albuminuria and reduced renal function, would appear, if not treated, to have a poor prognosis on the basis of our experience cited above (Griep, 1951). Of 11 patients in the study who fitted this description, 4 had survived the 10-year interval; the majority had died within 5 years.

Other urinary findings are of prognostic value. Gross or microscopic hematuria may indicate bleeding from the lower urinary tract or a serious exacerbation of the renal lesion Hyaline and granular casts are rare and appear in proportion as albuminuria and dehydration are present. Pyuria denotes the possible coexistence of pyelonephritis and requires careful consideration.

Because the renal excretory deficiency of hypertension is one of its most serious complications and one of the most difficult to treat, every effort should be made to identify renal functional deterioration before the onset of azotemia. When the signs and symptoms of renal excretory failure appear, established hypertension is usually converted into the malignant phase. Vascular deterioration and death follow rapidly. The relationship between renal failure and malignant hypertension is so close as to justify the presumption that prevention of renal excretory failure would go a long way toward eliminating malignant hypertension.

For these reasons, it is good practice to assess renal function at least once a year in any patient with severe hypertension. This may be done simply and effectively by measuring the 15-minute phenolsulfonphthalein excretion and examining the urine for albumin and for abnormal sediment. Detailed instructions for the performance of the phenolsulfonphthalein excretory test are outlined in Appendix 3, p. 262. If they are closely followed,

the test is reproducible within a few per cent on successive occasions and reductions of more than 5 per cent in excretory capacity may be considered significant. The normal excretory rate is 25–35 per cent in 15 minutes. Elevations in the blood nonprotein nitrogen level do not appear until excretory capacity has fallen to 10 per cent, or one third of normal. A hypothetical example of the use of the phenolsulfonphthalein test in following the renal vascular status of the hypertensive patient would be as follows: a patient with established hypertension excreted 30 per cent of injected phenolsulfonphthalein in 15 minutes on the first examination but on follow-up examination one year later showed on repeated testing an excretion of 20 per cent. Despite the lack of any significant elevation of nonprotein nitrogen in the interval, he would be considered to have a progressive renal complication of hypertensive disease.

Some evidences of renal functional impairment are present in most cases of established hypertension when tested by very elaborate methods. Among these first defects are increased excretion of sodium chloride and water in response to infusion of these substances (Cottier, 1958). The maximum excretory capacity of the renal tubules for para-aminohippurate and Diodrast is also reduced. At first, renal blood flow and glomerular filtration rates are normal, but slowly the former declines so that the fraction of blood filtered at the glomerulus is above normal in the earliest stages of hypertension (Goldring and Chasis, 1944). Later in the course of severe established hypertension, patients exhibit evidence of renal impairment that can be detected by simple clinical tests, but they usually maintain sufficient renal functional reserve to avoid azotemia more or less indefinitely. Measured by the most precise methods, renal plasma flow may fall to 200 ml. per minute and glomerular filtration rate to 40 ml. per minute. This represents approximately one third of normal renal function, or a level just above that at which significant azotemia would be expected to develop Measured in terms of renal function tests available to the average practitioner, one might summarize by saying that in essential hypertension urea clearance and phenolsulfonphthalein excretory capacity may fall to 30 per cent of normal but usually no further. Urine concentrating ability also shows some degree of impairment. In the average

case of severe hypertension these alterations occur very gradually unless the malignant phase supervenes.

THE MALIGNANT COMPLICATION OF HYPERTENSION

The clinical identification of malignant hypertension has been confused because of the variety of definitions given for it. In this text it is considered that papilledema and a diastolic pressure consistently elevated above the level of 130 mm. Hg will be required for the diagnosis of this condition. These are simple features to recognize and can lead to very little confusion in identifying the onset of this complication of hypertensive disease. Moreover, such a definition conforms in general to the initial description of Keith, Wagener, and Kernohan (1928). Since the retinal lesion is the first prerequisite for making the diagnosis and since one would like to be able to anticipate the development of malignant hypertension so as to institute effective treatment more promptly, it has become the custom in our hypertension clinic to recognize a premalignant phase in which there is some blurring of the disc margins and the appearance of one or more hemorrhages or fresh exudates. If these findings are associated with a very high blood pressure, it is certain that malignant hypertension is near at hand.

The malignant exacerbation should be looked upon as a most serious complication of essential hypertension which lies in wait for all severely hypertensive patients and is estimated to develop in 5 to 10 per cent. It usually follows or is accompanied by a progressive and severe rise in blood pressure from a previously lower level, a sharp decline in renal function, and the appearance in the urine of signs of active disease as manifested by increasing albuminuria, intermittent hematuria, or both.

OTHER CONSIDERATIONS IN THE PROGNOSTIC EVALUATION

Age

Generally speaking, the earlier the onset of hypertension the less favorable is the life expectancy. Mild established hypertension beginning in late middle life is rarely serious, while the

same degree of elevation in the young person is likely to affect his chances for living a normal life span. If hypertension is viewed as a condition in which elevated intra-arterial pressure leads to vascular degenerative disease, it is obvious that the longer a person's vessels are exposed to an increased tension, the more likely is the chance of a vascular accident.

Sex

In general, hypertension is tolerated better by women than by men. Therefore, in the male subject an equal degree of blood pressure elevation implies a worse prognosis and consequently, a more vigorous effort to reduce the blood pressure is indicated.

Race

It is generally believed that in the colored race diastolic hypertension is associated with a more serious prognosis than in the white person. There is a greater frequency of the malignant *exacerbation of the disease although the incidence of coronary* thrombosis is less in the colored than in the white male subject.

Family History

Occasional clinical studies support the common impression that *in hypertensive patients the prognosis is poor when there is a marked family history of early death from the complications of* vascular disease. This indicates the importance of the inheritance in explaining increased vulnerability of the arteries of some subjects to hypertension.

SUMMARY

A true estimate of the patient's usual blood pressure level is of great prognostic importance. This requires at least 5 to 6 casual blood pressure determinations supplemented in some cases by readings of the blood pressure in the home. On the basis of the patient's "usual" blood pressure, the hypertension may be classified as mild, moderate, or even severe and, according to the consistency of elevation, into a "labile" and an "established" category. The individual vascular vulnerability can only be estimated

by a careful search for evidence of vascular disease usually seen in one of four "target areas": in the retina, by focal and generalized retinal arterial constrictions, fresh hemorrhages, exudates, or papilledema; in the heart by evidences of left ventricular hypertrophy and angina pectoris; in the brain by focal cerebral episodes; and in the kidney by a progressive decline in renal function or by abnormal urine findings. Finally, malignant hypertension is defined and discussed as a generalized severe complication of hypertensive vascular disease with a particularly serious prognosis.

Certain general considerations may modify the prognosis in an individual case. It is recognized that, other factors being equal, survival in hypertensive disease is reduced when the subject is young, is of the male sex or colored race, or has a history of an increased incidence of vascular disease in the family.

SECTION IV

PRINCIPLES UNDERLYING THE TREATMENT OF PRIMARY HYPERTENSION AND OF ITS COMPLICATIONS



CHAPTER 11



Treatment of Hypertension Without Complications

The uncomplicated form of hypertensive disease includes by definition those cases in which the factor of vascular vulnerability is unknown, since no vascular complication has occurred. Such patients may remain indefinitely in this stage of the disease, their blood pressure may rise still further and a vascular complication develop, or after some years without change in blood pressure, vascular deterioration may finally appear. Since it is impossible to determine, when such a case is seen for the first time, what will be its course, two alternatives are available. First, one may simply keep the patient under close observation at intervals of 6 to 12 months, making careful records of blood pressure and examining the target organs for the appearance of vascular complications. The second approach is to assume that all hypertension is harmful, and to make every effort to reduce the blood pressure in the uncomplicated stage in the hope of preventing vascular deterioration. If therapeutic agents were available that would lower the blood pressure without side effects, the latter choice would be preferred. Unfortunately no effective regimen is entirely free from significant side effects and it is therefore necessary to justify the inconvenience of treatment in terms of necessity and to treat only those patients in whom the hypertensive risk is sufficient to justify the rigors of a long-continued antihypertensive program.

Table 8. Choice of Procedures in the Treatment of Hypertension Without Complications*

	Chlorothiazide and salt restriction	*Rauwolfia*	*Hydralazine*	*Mecamylamine*	*Sympathectomy*
Labile blood pressure	No	0	0	0	0
Labile hypertension					
Mild	No	0	0	0	0
Extreme	Yes	1	0	2	3
Established hypertension without complications					
Mild	Yes	1	0	0	0
Moderately severe	Yes	1	2	2	3
Severe	Yes	1	2	2	3

* Numerals indicate order of choice or of addition of treatment procedure for certain broad categories of hypertension. Two numerals of the same order indicate an equal choice between procedures or a combination of procedures. Chlorothiazide should be used in addition to all other treatment methods.

When a choice is to be made between observation without treatment and an attempt to lower the blood pressure, the cooperation and understanding of the patient are very necessary. It will be the thesis of this book that we must choose among four main forms of management of hypertensive disease.

1. No drug treatment but careful supervision of the individual patient with semiannual or annual follow-up to watch for progression of the disease.
2. The use of rauwolfia alkaloids and salt depletion in a carefully planned and executed manner.
3. The additional use of ganglion-blocking agents, especially mecamylamine, including in most instances the regulation of dosage by means of blood pressure determinations performed by the patient himself.
4. Sympathectomy.

The precise details of each treatment regimen are to be found in the Appendix, the theoretical aspects of each type of program are discussed in subsequent chapters. The choice of a treatment for patients with uncomplicated forms of hypertension is summarized in Table 8. The tabulation cannot, of course, provide a simple and complete answer for every patient. It is based on the form of the disease, the inconveniences of treatment, and other considerations to be discussed below.

MILD LABILE HYPERTENSION

The mild labile phase of hypertension can hardly be considered an immediate threat to the patient's health The reduction of blood pressure that might be achieved by treatment would not be of sufficient magnitude to offer much relief from the vascular strain of hypertension Anxiety concerning the presence of hypertension often worries the patient unnecessarily, since he may recall some severe or fatal complication in a friend or relative. To combat this natural reaction a program of lifetime supervision is planned with the patient and he is assured that treatment can be introduced when necessary to control the disease. The physician has the duty to inform the patient that he has hypertension, that with careful supervision his disease may never represent a

threat to him, and that actually, having discovered it in its early stages, he is in the fortunate position of being able to prevent a vascular complication by treatment of the condition should it ever become progressive. A careful initial examination for vascular disease should be performed (Appendix 4, p. 265) both for reassurance of the patient and as a base line for future comparison. The patient is informed that brief hypertensive episodes are *not* in themselves harmful and that the condition is benign but deserves conscientious follow-up. As further reassurance in the younger subjects, the author finds it advisable to review the study on Army officers with transient blood pressure elevation (Levy, 1947) in which the point is brought out that after 35 years the frequency of a serious vascular complication is increased by only 3 per cent over that expected in persons with normal blood pressure. It is then emphasized that the increased mortality rate occurred in an era when no effective therapy existed and that with the advantage of recognizing the disease from its inception, treatment may be planned so as to prevent even this 3 per cent increase in mortality over the 35-year period. If a lifetime program of supervision is then outlined to insure against missing the onset of a serious form of the disease, no reasonable person will develop a hypochondriacal reaction concerning his blood pressure. The regular scheduled follow-up is so important that a reminder is sent when the proposed check-up is due. If the patient should plan to leave the community or go under the care of another physician, he is given a letter containing his records.

Formerly in the practice of medicine it was customary to tell a mildly hypertensive patient nothing about his blood pressure, so as not to alarm him. On the other hand, if he knew that he had hypertension, he was often told to "forget about it" and that the fewer times he had his blood pressure taken the better off he would be. Despite this glib assurance, many patients developed fear neuroses concerning hypertension. Worse still, those who accepted the advice at face value often returned years later with an irreversible complication of hypertensive disease that might have been prevented. The program proposed in this book goes to the opposite extreme in frankness and in complete disclosure to the patient of his blood pressure and of his prognosis, since, in

contrast to former years, hypertensive disease is now controllable and the earlier that action is taken to this end, the better. Of further help to the patient in the mild labile stage of hypertension is the assurance that he may never acquire a more severe form of the disease; in fact, the older he is the less is there such a likelihood. If progression does occur, then only is suppressive treatment justified.

In view of the benign prognosis, it is not advisable to treat patients in the mild labile form of the disease with potent drugs There might be some justification if the systolic blood pressure often exceeds 160–170 mm. Hg and if treatment can be accomplished without inconvenience. Psychotherapeutic measures (p. 222), modest dietary salt restriction (p. 224), and perhaps the use of rauwolfia compounds (p. 197) and chlorothiazide (p. 285) would then be in order, but only if by such treatment the blood pressure is demonstrably reduced and side effects are completely absent.

EXTREME LABILE HYPERTENSION

Those patients who have on occasion had systolic blood pressure readings well in excess of 200 mm. Hg but usually have nearly normal blood pressures fall within the category of extreme labile hypertension. The prognosis in this condition is presumably midway between that of the mild labile and the established hypertensive groups. The outlook is generally good, since the blood pressure elevation is not continuously maintained and vascular deterioration is less likely to ensue. Symptoms may occur, however, particularly in the younger patient. The sharp rises in blood pressure are frequently attended by symptoms of vasomotor instability including headaches, palpitation, flushing, tremor, and nervousness. They may be spontaneous or induced by anxiety. Serious vascular complications rarely occur at this stage, but the patient often exhibits considerable concern both because he tends to remember the highest blood pressure readings that have been recorded and because he is unable to distinguish the truly premonitory symptoms of apoplexy or heart failure from the increased vasomotor activity that accompanies the highest blood pressures. The anxiety attendant upon testing

for pheochromocytoma may in itself raise the blood pressure. False positive histamine reactions occur especially in this group of patients. During the test or spontaneously, the patient may show a blotchy eruption about the face and neck. Such cases recall the diencephalic hypertension described by Page (1949) or the "neurogenic" hypertension of Schroeder (1953).

Since the prognosis is generally benign, the philosophy of *careful supervision but minimal efforts at treatment also applies to* this group. Reassurance of the patient should include emphasis on the frequency of near normal blood pressure readings, explanation that transient rises in pressure are not in themselves harmful, and a plan for careful long-term supervision to include repeated blood pressure determinations and a regular survey for vascular complications. In addition, rauwolfia alkaloids with or without chlorothiazide (Appendix 6, p. 197) are used, not only for their effect on the blood pressure but also to reduce the anxiety and tension that so commonly accompany this condition.

The elderly arteriosclerotic patient with extreme labile hypertension presents a different problem Here, perhaps because vascular changes incident to aging have already occurred, the acute rises in blood pressure may lead to cerebrovascular complications. The regimen of reassurance and rauwolfia administration in these older patients may be combined with small doses of mecamylamine (Appendix 7, p. 282) particularly in those who have had a focal cerebrovascular episode. Other details of the management of these cases will be found on p. 133.

MILD ESTABLISHED HYPERTENSION

Patients without vascular complications whose usual systolic blood pressure remains substantially below 200 mm Hg and does not vary markedly on random readings are classified in the group of mild established hypertension. Age and sex are important factors in the individual prognosis. For example, a male patient with a usual blood pressure of 180/100 mm. Hg at the age of 25 is more apt to experience a hypertensive complication of a serious nature before he has completed the period of his life expectancy than a 50-year-old woman whose hypertension had recently reached the same level. In the former, we have a lifetime ahead

and must undertake, if possible, to prevent the very likely development of a hypertensive accident in the next 20 years. In the latter case 20 years may well elapse before the disease would have taken its toll on the blood vessels and a nearly normal life expectancy would have been completed. Individuals of the first variety represent an important and serious therapeutic problem while the latter could well be reassured and discharged except for annual follow-up to guard against an unexpected rise in blood pressure or the development of a vascular lesion.

The management of the young person represents a problem of deepest concern since by treatment one may possibly prevent many of the complications of the disease. But such a potential effect requires a lifetime of suppressive therapy with its attendant cost, inconvenience, and side effects. It seems proper in this situation to combine careful explanation of the meaning of the disease and of its prognosis with the institution of a program of regular follow-up observations If necessary one may proceed later with a conscientious and thorough trial of reserpine with or without chlorothiazide (Appendix 6, p. 274). If the latter is effective, it should be maintained indefinitely with careful supervision to see that the blood pressure remains under control. If the drug is ineffective, two alternatives remain: either to proceed with more intensive measures, such as sympathectomy or the use of ganglion blocking agents, or to adopt a policy of watchful waiting for the possible development of a more progressive stage of the disease. Decision rests with the physician and with the patient. Usually a conservative program of supervision is planned. A period of home blood pressure recording may demonstrate that the readings that appear consistently high in a physician's office are in reality uncommon, and that at home he is usually subjected to pressures little above the normal range Such was the case in the example cited on p. 83. The use of surgical therapy or ganglion-blocking agents, if rauwolfia alkaloids are unsuccessful, is rarely advised unless the systolic blood pressure shows a clear rise to levels above 200 mm. Hg, or serious vascular disease appears in the heart, kidney, cerebral, or retinal system. Such an event will usually precede by 5 to 10 years any serious terminal complication of hypertension, and blood pressure control in this interval is likely to forestall a fatal outcome.

MODERATELY SEVERE ESTABLISHED HYPERTENSION

Patients with average systolic blood pressures consistently between levels of 200–240/110–130 mm. Hg but without vascular complications are placed in the group of moderately severe, established hypertension. If the diastolic blood pressure is above 110 mm. Hg, these patients fall within the category described in a previous prognostic study (Griep, 1951). Seventy to 80 per cent of such individuals will survive a 10-year interval. Twenty per cent will die of a vascular complication during such a period (see p. 78). The white male patient and the Negro patient will fare worse; that young persons may develop a serious lesion, such as malignant hypertension or cerebral hemorrhage, is the chief cause for apprehension.

The first two steps in treatment are obviously applicable here. The patient should be reassured, but one must insist on a repeated review of the blood pressure and particularly on repeated surveys of target organ function, since it will be remembered that the blood pressure is not likely to rise further but that vascular complications will be the first indication of a serious prognosis. The next therapeutic step consists of an intensive trial of rauwolfia alkaloids combined with chlorothiazide, in the hope of producing a significant and sustained blood pressure reduction. If a continued lowering of the average blood pressure to below 200/100 mm. Hg is achieved, the patient may be considered out of the "danger zone" with regard to cerebral hemorrhage. Other serious vascular lesions that might develop may be detected in the regular semiannual examination. Maintenance treatment with submaximal doses of rauwolfia alkaloid combined with careful supervision may be sufficient to prevent an uncontrolled rise in blood pressure, particularly among those patients in the "relatively safe" group as judged by such characteristics as age, sex, family history, and lack of progression of the hypertension.

If no reductions in blood pressure are secured with rauwolfia-chlorothiazide therapy, as will be the case in approximately 50 per cent of the patients, the decision to initiate the next step must be faced. We may now ask the patient to record his blood pressure readings at home for a few weeks. Only if this pro-

cedure provides evidence of a consistently elevated blood pressure *outside the office is it reasonable to consider a trial of* ganglion-blocking agents. Here again we should discriminate carefully between patients requiring immediate treatment and those whom we may be satisfied to follow for evidences of progressive disease. The young person with systolic blood pressure levels consistently above 200 mm. Hg and a correspondingly high diastolic reading should almost without fail undergo such a trial of treatment even if there are no other symptoms or complications of the disease at the time. By contrast, the middle-aged, obese white woman with the same blood pressure readings and the same general status may well be spared the rigors of more vigorous treatment methods if she will co-operate in a consistent follow-up program. We may in such a case err on the side of conservatism, since such patients may suddenly and unexpectedly fall victim to a cerebral vascular accident. To make a decision not to treat a patient with these drugs requires accepting a slight but definite risk for the sake of the patient's convenience. For these reasons it is good practice to discuss the problem fully with the patient and to explain that while vascular disease *is not yet manifest, the blood pressure is consistently* at the level where such lesions may develop. In this interview it is emphasized that probably the immediate course of the disease is benign even if the blood pressure cannot be well controlled. The nature of the suppressive treatment and the side effects to be expected are then *discussed frankly with the patient. The* conference is concluded by indicating that any treatment of the blood pressure at this stage is elective and that unless it is successful with a minimum of side effects, it will not be continued.

If the patient wishes to proceed with a trial of treatment, he is then instructed in the technique of *taking the standing blood* pressure at home, and asked to return in one or two weeks with a record of these readings. If the levels are still in the range observed in the office, chlorothiazide is prescribed, together with mecamylamine in very gradually increasing doses, in an effort to reduce the blood pressure *moderately while keeping side effects* to a minimum (Appendix 7, p. 278). A goal at the end of the first month *of treatment might be to achieve a usual systolic* standing blood pressure in the home of 160 to 180 mm. Hg.

More effective reduction might then be attempted if side effects permit. After three to four months of this regimen a reappraisal would be made both of the success of treatment and of the disability induced by the drug. The chart will show what has been accomplished in terms of reducing the blood pressure; the patient may have adapted to the side effects and be willing to continue in view of the tangible record of blood pressure reduction.

What effect such a program may have in preventing the development of vascular lesions is at present uncertain; but the recommendation is based on the likely presumption that high blood pressure by itself accelerates the development of vascular disease. No appropriate studies have been reported to prove that mecamylamine-induced blood pressure reduction in "benign hypertension" will prolong life. The median survival without treatment must exceed 12 to 15 years and few patients or physicians will be sufficiently conscientious to follow a program for so long a time.* Furthermore, despite the best of initial intentions, the expense of the program or discouragement over side effects will induce a large number of the patients to drop treatment entirely. While such an outcome is indeed regrettable, it does not excuse us as physicians from making every effort to emphasize the importance and justification of long-term blood pressure reduction. A similar situation exists when insulin is prescribed for control of a mild case of diabetes.

If even modest blood pressure reduction cannot be accomplished without very unpleasant side effects, it is important for us to recognize failure promptly so that our therapeutic enthusiasm does not go so far as to destroy the enjoyment of that very life that we are trying to prolong. Here indeed the "art and science" of medicine must unite. The initial premise on which the treatment was started must be recalled to the patient at the time of reappraisal. The disappointment of a therapeutic failure can be minimized by recalling that despite inability to reduce the blood pressure the disease is still judged benign. Continuity of management can be maintained by indicating to the patient

* Study of a very large number of patients over a shorter period might establish a statistically significant improvement of survival rate with treatment. A program of this sort has recently been introduced by certain Veterans Administration Hospitals. The results should prove of great interest.

that treatment can be reconsidered, possibly with newer drugs or with surgical techniques, should the semiannual survey demonstrate at some later date clear signs of progression of the disease to involve important target organs.

It is precisely at the point of such a therapeutic failure that many physicians often fail to make a proper decision. The patient is exposed successively to a variety of highly advertised treatments. With each conversion to a new drug or mixture, the anxiety of the patient respecting his future is increased and the rapport with his physician lessened. He now goes from one doctor to another or visits distant clinics, convinced that his blood pressure must be brought down or he will suffer serious consequences. With proper preparation of the patient for possible therapeutic failure this unfortunate conclusion may be avoided. It should always be held as a first principle that reduction of blood pressure in the benign stage of the disease would be advantageous but is by no means mandatory to survival. *For the* patient, failure to remain under medical observation is the one dangerous course of action.

Lack of a satisfactory response to mecamylamine is often more apparent than real. In the Hypertension Clinic only 20 to 30 per cent of patients who were placed on mecamylamine treatment alone proved refractory, although many of them had been referred *specifically because their* blood pressure "failed to respond" to this same drug (Cottier, 1957). Apparent failures to respond were frequently the result of reliance on blood pressure readings obtained only in the office or clinic. If home records of the standing blood pressure before and after treatment are compared, and if chlorothiazide is also administered, reduction of blood pressure will occur in almost every case without prohibitive side effects. Recumbent blood pressure is less commonly reduced. "Dizziness" in the upright posture is frequently given as a reason for treatment failure This symptom naturally follows attempts to normalize the blood pressure in the sitting or recumbent position, but occurs less commonly when treatment is directed toward maintaining a normal standing blood pressure. The other chief reason for alleged treatment failure has to do with inadequate control of bowel function. Most patients do not use *laxatives with sufficient frequency and effectiveness, conse-*

quently they give up before an adequate dose of the drug has been reached. It is necessary to insist on regular use of laxatives particularly during the initial stages of treatment with mecamylamine.

SEVERE ESTABLISHED HYPERTENSION WITHOUT COMPLICATIONS

By prior definition a patient with office blood pressure readings usually exceeding 240/130 mm. Hg would fall in this category if no evidence of vascular complications had appeared and if blood pressure readings in the home were also markedly elevated. The middle-aged, obese female often appears to sustain such an elevation for long periods with little vascular involvement, but in others complications occur after a few years.

In general, patients in this category deserve vigorous treatment since cerebral hemorrhage is an ever-present and quite unpredictable danger. If mecamylamine is ineffective, sympathectomy may well be recommended.

TREATMENT OF SYMPTOMS ASSOCIATED WITH RELATIVELY BENIGN HYPERTENSION

Occasionally a hypertensive symptom not denoting a vascular complication may coexist with one of the above-mentioned forms of mild hypertension. This symptom may be a morning headache or an occasional dizzy spell. In those cases with labile blood pressure episodes of vasomotor instability with palpitation, flushing, tremor, and marked anxiety frequently appear. These symptoms together with headache can usually be effectively managed by the use of salt restriction and chlorothiazide or rauwolfia alkaloids. If such a program is ineffective, small doses of ganglion-blocking agents are often sufficient for relief. This modified regimen, described in Appendix 7, p. 283, may be useful when a symptom needs relief but a major effect on the blood pressure is not desired. Dizziness and mental confusion occurring on a similar basis may likewise respond to such treatment.

Fatigue, which is a common complaint particularly in hypertensive women, cannot be greatly improved. If the fatigue is

largely due to nervous apprehension, the tranquilizing effect of rauwolfia may be of assistance but usually reserpine itself aggravates this symptom. Ganglion-blocking agents, even in small doses, are not helpful.

The complex of vasomotor symptoms commonly associated with hypertensive episodes in the labile phase of the disease can frequently be reduced or prevented by the use of rauwolfia alkaloids. In some instances these symptoms in themselves and the anxiety they produce are sufficient to justify the use of stronger measures. Either sympathectomy or ganglion-blocking agents are often effective, but the benefit to be derived from relief of such episodes must be weighed against the side effects to be produced by such a program.

Epistaxis and menorrhagia when related to hypertension are usually associated with considerable elevations of the blood pressure. Although these symptoms have not been listed as serious vascular complications, their presence usually is a warning that the hypertension is of sufficient severity to warrant vigorous efforts at blood pressure control. In general, patients with such symptoms should be treated until the blood pressure is brought to near normal levels with chlorothiazide and either rauwolfia alkaloids or mecamylamine. Sometimes nasal congestion following reserpine increases the frequency of nasal hemorrhage, but usually these symptoms do not recur on an effective antihypertensive program. The emergency program for uncontrollable bleeding in a hypertensive subject is summarized in Appendix 5, p. 266.

SUMMARY

The management of patients with uncomplicated essential hypertension is described. In all cases full and complete discussion with the patient and the institution of a careful follow-up program are advocated. After consideration of blood pressure status and the age, sex, and personality of the individual patient, various treatment regimens are prescribed, usually in the following order: (1) reassurance, careful supervision, and regular follow-up; (2) administration of rauwolfia alkaloids and chlorothiazide to those who show blood pressures in excess of 180 mm. Hg systolic and to many with the mild established or extremely

labile forms of the disease, particularly in the younger age group; (3) use of ganglion-blocking agents, such as mecamylamine with chlorothiazide, in young patients with more severe forms of hypertension if the treatment is well tolerated. In the case of the severely hypertensive patient, with blood pressure usually exceeding 240/130 mm. Hg, drug treatment is mandatory, and if it is unsuccessful in reducing the blood pressure, sympathectomy or various combination programs should be advised.

The aim in all instances is to reduce the blood pressure modestly and in a way consistent with normal living habits. In the case of mecamylamine this requires painstaking attention to detail and careful recording of blood pressures in the home.

If the standing systolic blood pressure can be maintained continuously below 200 mm. Hg, a cerebral hemorrhage is unlikely and more vigorous treatment may not be necessary unless vascular complications appear on follow-up examination. Such a treatment objective can usually be accomplished without serious side effects.



CHAPTER 12



Treatment of Established Hypertension With Congestive Heart Failure

REDUCTION OF THE BLOOD PRESSURE

When left ventricular failure is associated with established hypertension, antihypertensive drugs may be most useful in the treatment of the attack and in the prevention of recurrences. Successful prevention of attacks requires prompt and effective control of the blood pressure. In acute emergencies the program outlined in Appendix 5, p. 266 should be followed Long-continued treatment requires the use of chlorothiazide and mecamylamine combined with blood pressure readings in the home to assure adequate control. The therapeutic regimen is outlined in Appendix 7, p 278. If the treatment is effective, paroxysmal nocturnal dyspnea or dyspnea on exertion should cease. If they do not respond, two alternate explanations are in order: first, that the heart has been so much damaged by vascular disease that the primary component in its failure is "arteriosclerotic" rather than the mechanical work load of hypertension, or secondly, that the hypertension is of such severity that without concomitant reduction in the recumbent blood pressure, left ventricular failure will continue to occur. Since the recumbent blood pressure of patients treated with ganglion-blocking agents is not greatly reduced, paroxysmal nocturnal dyspnea might in theory prove refrac-

tory to treatment. Nevertheless, this symptom is often relieved despite a continued high arterial pressure in recumbency. Perhaps blockade of venous tone by the drug provides an enlarged venous reservoir and thus achieves a bloodless phlebotomy into the venous system, thereby protecting the lungs at night from overload. In the rare case where orthopnea or nocturnal dyspnea resists conventional treatment, it may be advisable to try a larger dose of the drug just before bedtime, to attempt to increase the ganglionic blockade during the period of increased risk from nocturnal pulmonary edema. The increased dose may be so great as to produce severe orthostatic hypotension if the patient arises in the night. He must be warned of this possibility. In patients with milder degrees of hypertension a relatively small single evening dose may be sufficient to prevent nocturnal dyspnea and to maintain continued orthostatic hypotension of just the proper degree throughout the day. Such a regimen is described in Appendix 7, p. 282.

With effective treatment, the signs and laboratory findings of cardiac failure improve only slowly since they have been established as a result of many years of hypertension. Although a gallop rhythm may promptly disappear as compensation is reestablished, T wave inversion and axis deviation in the electrocardiogram and cardiac dilation as demonstrated by x-ray improve more slowly following effective regimens for blood pressure reduction.

Patients who have a marked elevation of the blood pressure are of special interest only in association with congestive failure. This condition may represent a special form of salt and water-dependent hypertension, so-called "stasic hypertension" (Fishberg, 1954). In such cases, the elevated blood pressure will fall to normal if the patient is rendered free of edema. In any event, diuresis should first be induced with chlorothiazide or mercurials, and after the edema has cleared, control of the blood pressure may be instituted if necessary. If the patient fails to respond to the diuretic, antihypertensive medication should be given for symptomatic relief and to promote diuresis. If the patient develops congestive heart failure with edema while he is receiving ganglion-blocking drugs, these should be continued during the administration of the diuretic. However, the

combination of a diuretic agent and mecamylamine leads to sensitization to the ganglion-blocking agent, apparently as a result of extracellular fluid depletion, since the increased responsiveness does not occur unless weight loss is produced by the diuretic. This phenomenon was originally observed when mercurial injections were given to patients receiving ganglion-blocking drugs The oral diuretic agent chlorothiazide also appears to sensitize to the hypotensive effects of ganglion-blocking drugs. This observation has two useful applications. In an edema-free hypertensive patient, apparently refractory to mecamylamine but without signs of congestive heart failure, administration of a diuretic such as chlorothiazide may cause the excretion of sufficient fluid to make his blood pressure responsive to ganglionic blockade. Furthermore, the administration of such a diuretic to patients responding well to ganglion-blocking agents may require considerable reductions in the usual dose if severe postural hypotension is to be avoided. It is, of course, very desirable to achieve satisfactory orthostatic hypotension with smaller doses of ganglion-blocking agents and with correspondingly lessened parasympathetic side effects. The technique of combining chlorothiazide with mecamylamine is described in Appendix 7, p. 279.

The following case history shows the usefulness of such a regimen in combating mecamylamine resistance even when edema is not apparent.

Case History

A 53-year-old university professor came to the Hypertension Clinic with the complaint of uncontrolled hypertension for 2 years and recent mild dyspnea on exertion. He had previously been hospitalized for incipient heart failure with paroxysmal nocturnal dyspnea.

Casual blood pressure was 212/120 mm. Hg and 180/110 mm. standing. The funduscopic examination revealed focal retinal arterial vasoconstriction, hemorrhages, and fresh exudates without papilledema. The heart was enlarged to percussion. The liver was barely palpable at the costal margin.

Treatment with mecamylamine was commenced and the drug was *gradually increased to 10 mg. three times daily*, with a con-

sequent effect on the daily afternoon standing blood pressure such that it varied between 128/92 mm. Hg and 154/106 mm. and between 204/114 mm. and 243/128 mm. recumbent. At this time an unexpected resistance to the drug set in without any change in symptoms or general level of well-being. The standing blood pressure now remained between 192/134 mm. Hg and 210/140 mm. After several weeks the patient noted the onset of numbness of the right hand and difficulty with speech. In the clinic the blood pressure was 243/128 mm. Hg casual, 214/126 mm. resting, and 240/120 mm. standing. Examination at this time revealed no edema, hepatic enlargement, or cardiac failure. There was some weakness of the right side of the face. The patient was given chlorothiazide, 500 mg. 4 times daily. The standing blood pressure fell the first day to 142/98 mm. Hg and was 126/88 mm. and 136/100 mm. on the next two successive afternoons. The recumbent blood pressure was 204/114 mm. Hg. He experienced a marked diuresis with a loss of 4 pounds in 3 days He continued to take chlorothiazide and mecamylamine, *and the daily standing blood pressures remained within normal* limits. When the diuretic was inadvertently discontinued there was a prompt gain of 4 pounds in weight and a rise in the standing blood pressure to 240/120 mm. Hg. Satisfactory control was again achieved by prescribing chlorothiazide and the patient has been maintained on this regimen successfully for 8 months.

COMMENT. Loss of sensitivity to mecamylamine developed unexpectedly in this patient with cardiac weakness but no evident edema. With the loss of 4 pounds of fluid, the blood pressure in the upright posture was normalized A rapid and potentially dangerous rebound occurred when the diuretic was discontinued. The patient has remained under good control on a greatly reduced dose of mecamylamine with fewer side effects and a great improvement in general well-being.

Other antihypertensive drugs have, of course, been used for continued treatment of hypertension associated with cardiac failure. *Rauwolfia alkaloids* by the parenteral route may be helpful, but for chronic use they do not bring about a sufficient blood pressure decline and may even lead to some salt and water retention. They are rarely used alone in the management of cardiac failure.

Theoretically, one of the most effective drugs should be *protoveratrine*, which reduces blood pressure, slows the heart, and may in addition have a cardiotonic action. In the era before mecamylamine this drug was found particularly effective in treating hypertensive heart failure (Hoobler, 1952) and only because of difficulty in dosage adjustment has it been abandoned. The oral administration of protoveratrine is harmless if its effects on cardiac rhythm are closely followed. It clearly deserves trial in a hypertensive cardiac patient who is refractory to ganglion-blocking agents and chlorothiazide. No instance in which the blood pressure has been unaffected by veratrum has been observed in the Hypertension Clinic, even in patients totally unresponsive to large parenteral doses of pentolinium Details of a regimen for the chronic administration of protoveratrine are to be found in Appendix 8, p. 289.

Hydralazine causes many side effects that resemble those of congestive heart failure It increases cardiac output and may precipitate coronary insufficiency in addition. However, some investigators recommend its use alone or in combination with ganglion-blocking agents for hypertension with heart failure (see Appendix 9, p. 294; Appendix 11, p. 299). In the University of Michigan Hypertension Clinic hydralazine has been found unsuccessful in the management of this complication and has been entirely superseded by mecamylamine with or without chlorothiazide.

SYMPTOMS CAUSED BY TREATMENT

Dyspnea

Occasionally a patient whose standing blood pressure is under exceptionally good control with mecamylamine will have an excessive fall in blood pressure on activity or after motionless standing for considerable periods. As a consequence, cerebral hypoxia will occur of which one of the symptoms is breathlessness. When this occurs after exercise, it may be mistaken for cardiac dyspnea. This form of dyspnea can usually be identified by asking the patient to record his upright blood pressure during such an episode, or by taking such a reading in the clinic after light exercise. Individuals who have had a sympathectomy are especially prone to this type of complaint when ganglion-blocking

agents are added to the therapeutic program. Dyspnea may also be the chief complaint of a patient suffering from the flatulence that often follows the use of ganglion-blocking drugs. This may occasionally occur despite regular bowel movements, and it requires an alteration in the laxative program or omission of the blocking agent.

In an occasional patient, standard doses of rauwolfia alkaloid will produce an unexplained hyperpnea and dyspnea but this condition is more commonly found only in patients receiving excessive amounts. This type of dyspnea has no relation to posture or activity and is thereby easily distinguished from left ventricular failure. It appears to be a hyperpnea of central origin.

When hexamethonium was administered in large doses over long periods of time to azotemic hypertensive patients, a usually fatal syndrome sometimes appeared (Perry, 1957). The symptoms included extreme dyspnea in the seated or standing position and relief on assuming recumbency. Careful studies of this phenomenon have been reported (Parke, 1956). Because of its invariable association with uremia, the syndrome is believed to be a consequence of uremic pneumonitis in which some degree of pulmonary fibrosis has followed retention of dried and inspissated bronchial secretions. The reason for the peculiar dependence on posture has not been clearly explained. This condition has not so far been described in association with other ganglion-blocking agents and may be a specific effect of hexamethonium.

Edema

The chronic use of mecamylamine may cause edema, which may appear only after a considerable period of effective treatment in a patient who has never previously exhibited signs of cardiac failure. It has also occurred to a lesser extent with other ganglion-blocking agents, but the fact that it is seen more frequently with mecamylamine presumably indicates that, in general, blood pressure control is more effective with this drug. The condition responds to diuretics and should be largely preventable by maintenance treatment with chlorothiazide. Inferential evidence suggesting that the edema is due to salt and water retention following effective blood pressure reduction is as follows: (1) Blood pressure reduction with ganglion-blocking agents has

been shown to reduce salt and water excretion (Moyer, 1956a). (2) Most patients who take ganglion-blocking drugs experience a diuresis at night which suggests a loss of salt and water when their blood pressure rises in bed. (3) Cases in which the blood pressure is most effectively controlled are the most likely to develop edema, perhaps because night-time elimination of salt and water falls behind day-time retention. (4) The condition is aggravated by an increase in salt intake and improved by extreme sodium restriction. (5) The edema is not associated with any measurable increase in any of the symptoms, physical findings, or laboratory indices of congestive heart failure.

Edema can also be produced by several other hypertensive drugs. Puffiness of the face and definite weight gain have been observed after the use of rauwolfia alkaloids. Perera (1955) demonstrated the production of edema by the use of this agent and its disappearance following treatment withdrawal. The mechanism of action is not clear but it is conceivably related to sodium and water retention and may be a further indication that rauwolfia alkaloids are not particularly suitable in the treatment of patients with hypertension who are in impending or actual congestive failure.

A peculiar edematous syndrome that may follow hydralazine but is not related to the precipitation of congestive failure is well known. Sometimes it occurs in the absence of other side effects and apparently is the consequence of some effect of the drug on capillary permeability.

Case History

A 49-year-old colored man was admitted to the hospital because of the sudden onset of marked edema of the legs He had known hypertension for two years without any other symptoms of cardiac failure. For 11 months he had received mecamylamine with good control of the blood pressure in the standing position. Hydralazine was added to his regimen in the hope of reducing the recumbent blood pressure. After 8 days of treatment with the drug at a dosage level of 25 mg. 3 times daily, he called to complain of marked edema of the legs. He was reassured and asked to continue with the drug. He returned 9 days

later with four-plus pitting edema of both legs and was immediately admitted to the hospital.

The patient was able to lie flat without distress. The recumbent blood pressure was 220/120 mm. Hg. The heart was enlarged but the liver was not palpable. The neck veins were not distended. The lungs were clear. There was massive edema of the lower extremities. Urinalysis revealed three plus albuminuria; electrolytes and serum protein were within normal limits except for an albumen of 3.5 Gm. per 100 ml. Serum cholesterol was 120 mg. per cent; creatinine 4 32 mg. per cent with a clearance of 23 liters per 24 hours. The 24-hour urine protein was less than 1 Gm. Chest films showed a slight increase in cardiac size from one year previously, when it had been considered normal.

The patient responded to conventional diuretics with a 30-pound weight loss. Hydralazine was discontinued. He was followed in the clinic for 8 months without recurrence of edema.

COMMENT. The nature of the massive edema was never explained, but the temporal relation to hydralazine administration and the lack of significant evidence of left heart failure suggests that an abrupt alteration in vascular permeability was a factor in its production. No other cases of equally severe edema have been observed, but lesser degrees of unexplained ankle edema have occasionally followed hydralazine therapy.

Palpitation

Palpitation and tachycardia occasionally follow the use of hydralazine. These symptoms may also accompany the postural hypotension of certain patients receiving ganglion-blocking agents, in which case the symptom is observed by the patient only when in the erect posture. In some instances the rapid heart action is readily perceived by the patient; on other occasions palpitation is not recognized with the drop in blood pressure, and syncope may ensue without warning.

Chest Pain

Substernal pain is not commonly associated with the antihypertensive agents in common use. However, an occasional pa-

tient with angina pectoris will complain of more frequent pain when the blood pressure is lowered, and in such a patient antihypertensive treatment must be prescribed with care. If the first goal of therapy is deliberately restricted to producing a very slight fall in the blood pressure, the coronary circulation seems to adapt so that at a later date more substantial reductions can be achieved without precipitating angina. When angina is consistently increased by treatment, the patient should be warned to proceed more slowly in lowering the blood pressure.

Veratrum compounds produce regularly a peculiar, not unpleasant, substernal burning sensation experienced 20 to 50 minutes after ingestion of the drug. The symptom passes away some time before the drop in blood pressure occurs. The sensation also appears in the mouth and throat and is probably the result of afferent stimulation of the cells of the nodose ganglion. It comes on immediately following intravenous administration of protoveratrine or other veratrum derivatives. If this side effect of the drug is recognized, fear of impending coronary insufficiency may be allayed. The appearance of an excessive amount of substernal burning after an oral dose of the drug suggests that an excessive fall in blood pressure may occur later.

OTHER FORMS OF TREATMENT

It goes without saying that in the treatment of actual or impending heart failure all methods at the physician's disposal should be used. For a more complete discussion of other forms of management of heart failure the reader is referred to standard texts on the subject. However, for the sake of completeness conventional management will be discussed briefly.

Weight Reduction and Salt Restricted Diets

In obese cardiac patients weight reduction will be of great help in managing the condition. While moderate salt restriction is recommended for all hypertensive patients, it is particularly important in the management of the patient with cardiac failure. Sometimes it is necessary to prescribe a 200 mg. sodium diet to obtain the maximum benefit from salt restriction. Less rigid restriction is necessary if one recommends an effective "desalting

program" consisting of the administration of chlorothiazide 0 5 Gm. 3 to 4 times daily for 3 days, followed by maintenance treatment with 0.5 Gm. twice daily. Alternatively the drug may be used only when weight gain or edema reappears. If this treatment is ineffective or produces signs of hyponatremia or hypochloremia, a course of ammonium chloride, 3 Gm. three times daily for three days, followed by a mercurial diuretic, usually removes occult edema from the hypertensive patient with signs of impending left ventricular failure. It may also be given a therapeutic trial in patients with nocturnal dyspnea. The amount of weight lost in retrospect indicates the importance of fluid retention as a cause of the patient's original complaint. A normal person will rarely lose more than two or three pounds after such a program, so that weight loss in excess of this indicates excessive fluid retention. Dehydration will usually make the blood pressure more responsive to ganglion-blocking drugs If antihypertensive drugs have not been prescribed, it is best to withhold this treatment until the minimum weight has been reached. By then the blood pressure may well have fallen to a level at which no immediate treatment is necessary. The patient should then be discharged home on a regimen of salt restriction with or without chlorothiazide, and directed to watch his weight carefully. If the blood pressure rises despite a continued absence of fluid retention, further antihypertensive treatment may be prescribed. However, it is surprising how frequently a program of conscientious sodium restriction combined with chlorothiazide may alone maintain blood pressure reduction and cardiac competence in hypertensive patients with a history of congestive failure.

USE OF CARDIAC STIMULANTS

Digitalis should not be withheld from hypertensive patients with a large heart or early signs of circulatory failure. If rapid initiation of treatment is desired, a single dose of 1.2 mg. of digitoxin may be given and followed by the use of digitalis leaf, 0.1 Gm. daily. The rationale of the procedure is to obtain full digitalization without gastrointestinal side effects, but to protect against the late toxicity often seen after the chronic use of digitoxin.

Although more properly considered under the chapter on hypertensive emergencies, the prophylactic use of aminophylline for bouts of pulmonary edema should be mentioned. Unfortunately, this is an unpredictable complication in which medical attention may be needed in the middle of the night, when it is least available. The most effective self-treatment for this complication is the use of rectally instilled theophylline or aminophylline.* Experience with this technique of administration has revealed that it is approximately as effective as intravenous administration, is much superior to the suppository in speed and effectiveness, and has the great advantage that it can be used by the patient to obtain instant relief when he most needs it. It is now routine in our clinic to provide patients susceptible to nocturnal dyspnea with a supply of rectal aminophylline for emergency use during attacks of pulmonary edema.

SUMMARY

Left ventricular failure associated with severe hypertension is greatly relieved by an effective antihypertensive program in combination with cardiac stimulants and diuretics. Loss of salt and water by the cardiac patient may lower his blood pressure and sensitize him to the action of ganglion-blocking agents. Symptoms of cardiac insufficiency should be relieved by effective blood pressure reduction except when there is considerable myocardial disease or when the drugs employed to lower the blood pressure may of themselves have side effects that result in the production of dyspnea, edema, palpitation, or chest pain.

* A disposable plastic bottle for rectal instillation is made by the C B. Fleet Company, Lynchburg, Va It contains a single effective dose of Monotheamin, a theophylline derivative that does not produce rectal irritation It is marketed under the trade name "Clysmathane."



CHAPTER 13



Treatment of Established Hypertension With Coronary Insufficiency

REDUCTION OF THE BLOOD PRESSURE

HYPERTENSIVE PRECORDIAL PAIN

A syndrome occurring more often in female patients with severe hypertension is one that resembles atypical angina pectoris. Reasons have been given elsewhere (p. 91) for the opinion that this syndrome is caused by the excessive cardiac work associated with extreme elevation of blood pressure and relatively inadequate coronary flow. To differentiate it from typical angina pectoris the syndrome has been described as "hypertensive precordial pain." Striking relief follows any treatment that lowers the blood pressure, such as salt restriction or the use of rauwolfia alkaloids or ganglion-blocking drugs. Hydralazine is contraindicated because it increases cardiac work.

ANGINA PECTORIS

Typical angina pectoris occurring in the severely hypertensive patient is unusual but when it does develop it may be benefited by careful gradual reduction in blood pressure by means of rauwolfia and ganglion-blocking drugs. The enthusiastic claims

of some investigators for the consistent relief of angina by the use of these agents seem overoptimistic. Perhaps skepticism is derived from the experience of seeing no apparent reduction in the number of cases of coronary thrombosis during effective antihypertensive treatment. However, since ganglion-blocking drugs have been shown to reduce cardiac work, it might be expected that they would relieve angina pectoris if an excessive reduction in coronary perfusion pressure could be avoided. The importance of careful supervision of antihypertensive treatment is illustrated by the following case history.

Case History

A 50-year-old man was admitted to the hospital with a 5-year history of hypertension and the more recent complaint of substernal chest pain after exertion, relieved by nitroglycerine. Except for a blood pressure reading of 200/110 mm. Hg, a slight cardiac enlargement, and Grade II retinal arteriosclerosis, the results of the physical examination were within normal limits. The electrocardiogram showed only T wave inversion in leads I and II. The anginal pain occurred once or twice daily on mild activity in the hospital ward. Administration of mecamylamine was started in a dosage of 0.5 mg. twice daily and this was followed by abrupt reduction of the standing blood pressure to 150/100 mm. Hg. The symptoms of angina occurred with greatly increased frequency. Treatment was interrupted and the blood pressure permitted to rise to 170/120 mm. Hg. Chest pain became less frequent Blood pressure reduction was again induced, but even more gradually, until finally a level of 120/90 mm. Hg was reached without increasing the severity of the angina pectoris. When the patient returned to the clinic a month after his discharge from the hospital, he reported that the attacks of angina were much less frequent so long as he was able to maintain his blood pressure at near normal levels.

COMMENT. While the initial acute reduction in blood pressure increased the severity of angina pectoris in this patient, a more gradual decline in blood pressure resulted in considerable improvement in the coronary pain. It would seem that after a

period of adaptation, coronary perfusion rate returned to normal despite the considerable reduction in blood pressure.

Typical angina pectoris is more common in the patient with mild established hypertension, and the use of potent antihypertensive drugs in this situation is not advisable. The extent of blood pressure reduction that can be secured in such mildly hypertensive individuals is not great enough to lead to improvement in the angina. Consequently, ganglion-blocking drugs are not recommended, and for similar reasons, veratrum alkaloids also are contraindicated. Reserpine, which slowly decreases the pulse rate, may improve coronary flow somewhat by prolonging the interval of diastolic filling. The drug has been reported to be of considerable benefit in angina pectoris. Success in the treatment of this condition with reserpine has rarely been observed in our hypertension clinic Hydralazine is contraindicated because it increases cardiac output and cardiac work (Rowe, 1955).

CORONARY THROMBOSIS

Acute coronary thrombosis is not often associated with severe hypertension. This is fortunate, for in this serious condition the problem of adjusting the blood pressure level is very difficult. While it is desirable to relieve cardiac work as far as possible, one fears to reduce perfusion pressure in coronary arteries already narrowed by disease. Furthermore, depressor drugs may aggravate the shock stage that sometimes follows a serious myocardial infarction. Usually bed rest, sedative agents, and parenteral reserpine are sufficient to control the blood pressure. If the coronary thrombosis occurs in a patient already under antihypertensive treatment, and if the blood pressure might rise excessively on withdrawal, the drug should be continued to avoid adding a hypertensive rebound to the other complications of this serious condition. Moreover, if anticoagulants are to be administered during the acute myocardial infarction, and the hypertension is very prominent, the risk of a cerebrovascular hemorrhage is a further reason for maintaining some reduction in blood pressure. Antihypertensive treatment is probably indicated when the blood pressure is above 200 mm. Hg after several days of bed rest, in most cases of myocardial infarction.

After the patient has passed the critical stage of coronary thrombosis, he should be treated with antihypertensive medication if his pressure remains high and particularly if chronic anticoagulant treatment is planned. Rauwolfia alkaloids and chlorothiazide should first be tried, and followed if necessary by the cautious administration of ganglion-blocking drugs. These should be given in such slowly increasing doses as never to risk the production of extreme orthostatic hypotension. While blood pressure reduction lasting only for a period of several months appears to have little effect on the frequency of coronary thrombosis, it is possible that prolonged treatment of hypertension in its early phases might protect against coronary vascular disease. Coronary thrombosis does not usually occur in women unless hypertension or some other atherogenic process is present, it occurs three times as frequently in middle-aged men with even slight degrees of hypertension (Dawber, 1957), suggesting that blood pressure elevation is an important factor in the evolution of this complication. Prolonged remission of angina pectoris in a few of our young male patients whose blood pressure has been effectively controlled provides further evidence for this view. Perhaps one of the ultimate benefits to be derived from effective treatment of established hypertension from the moment of its inception is the prevention of coronary artery disease. Just as the accumulation of coronary atheromata is undoubtedly a very slow process, prevention of further accumulation or dissolution of a formed lesion within the coronary artery is likely to be so slow that treatment which begins only after these complications have occurred can hardly be expected to improve the prognosis. Only a long and carefully controlled study might demonstrate that the early treatment of hypertension would reduce the incidence of coronary artery disease in these patients.

OTHER METHODS FOR THE TREATMENT OF CORONARY DISEASE

The liberal use of nitroglycerine is still the mainstay in the treatment and prevention of attacks of angina pectoris. Coronary vasodilators given by the oral route have not appeared in our experience to be of much prophylactic or therapeutic value.

Many of these drugs are marketed with the added claim that they are effective in lowering the blood pressure. In most instances their depressor properties are so feeble as to be of little value. However, a weak depressor drug may become effective when the buffer reflexes are interfered with by ganglion-blocking agents. Thus nitroglycerine given to an untreated hypertensive patient usually produces only a transient and insignificant reduction in blood pressure. When the same patient is under the effects of ganglion blockade, sublingual nitroglycerine may reduce the standing blood pressure to the point of orthostatic syncope. Consequently a patient under the influence of a ganglion-blocking agent should sit or lie down before taking nitroglycerine for anginal pain. When longer-acting nitrates and nitrites are prescribed, concomitant ganglion blockade does not usually cause an excessive blood pressure decline but theoretically the possibility exists that such a drug combination might produce adverse effects in certain particularly sensitive individuals.

For refractory cases of angina pectoris, several regimens have proved successful. For acute continuous anginal pain, large doses of intravenous aminophylline may be very useful as a therapeutic or diagnostic procedure. When status anginosus appears to be present, an initial injection of 500 mg. of aminophylline in 10 minutes if followed by an infusion of 500 to 1,000 mg. over the next 2 to 4 hours will regularly relieve the anginal pain not only for the period of the infusion but also for a subsequent 12- to 24-hour interval. The rate of infusion must be adjusted below the level that produces nausea, and some supervision of the blood pressure is also necessary. Likewise the daily rectal instillation of aminophylline solution in the morning may prevent severe recurrent attacks of angina pectoris during the next few hours. The disagreeable side effects of this drug when taken by mouth are avoided by such administration, and inactivation by the liver occurs more slowly. As a solution for rectal administration, it is better tolerated and more effective than as the suppository. It should be administered upon awakening, and a period allowed for absorption before the patient arises. The use of a plastic bottle with rectal applicator ("Clysmathane," p. 125) reduces the inconvenience of the procedure.

Another program for the management of intractable angina pectoris involves administering enough radioactive iodine to reduce the metabolic load on the heart but not enough to induce a state of true myxedema. More than half of patients are favorably influenced by this treatment. The reader is referred to the report by Blumgart (1952) for further details. In a few cases with very high erythrocyte counts, erythropoetic activity has been depressed by P^{32} treatment. In patients with hematocrit readings above 55 and severe angina pectoris, symptomatic relief has accompanied reduction of the hematocrit to a level of 40 to 45 per cent. Although this treatment will need further evaluation before it can be applied generally, it does have the advantage of safety and relative simplicity.

Surgical procedures, including cardiac sympathectomy and pericardial operations, have been advocated for the treatment of angina pectoris. Although these procedures bear some promise, the high mortality rate is a considerable deterrent, and medical management seems preferable in most cases.

Continuous oral anticoagulant treatment is advisable for severe and progressive angina pectoris and extensive myocardial infarction, on the theoretical ground that impending coronary thrombosis may be avoided but not in expectation of much relief of the angina. This regimen may be employed without fear of cerebral hemorrhage in hypertensive patients with systolic blood pressures below 200 mm. Hg.

Reduction in blood cholesterol levels certainly seems desirable in the prophylactic treatment of coronary disease. Beta-sitosterol (Cytellin, Lilly) will cause some reduction in serum cholesterol. While this agent can reduce the size of xanthelasmas in patients or prevent atheroma formation in the cholesterol-fed rabbit, it has little effect on anginal pain and should be prescribed for its possible, but as yet uncertain, long-term benefits.

A similar argument may be applied to heparin, unsaturated fats, and other preparations designed to lower cholesterol levels or alter blood lipids. While there is good theoretical basis for such treatment, relief of angina pectoris is negligible and no evidence has been offered that such programs reduce the death rate from coronary disease. In the light of present knowledge it is best that such regimens be prescribed only by the clinical investiga-

tor; if the treatment is advised by the general practitioner, the regimen should be one that cannot be nutritionally or psychologically harmful, since the beneficial effects of such prolonged treatment have not been proved.

SUMMARY

The syndrome of hypertensive precordial pain has been described and differentiated from typical angina pectoris. Blood pressure reduction is more effective in relieving the former condition. Antihypertensive drugs should be used very cautiously in angina pectoris but sometimes provide relief from pain. The relation between hypertension and coronary vascular disease is discussed. The hypertension associated with acute myocardial infarction should be managed conservatively, but after the acute episode has passed there is no contraindication to the use of antihypertensive drugs.

CHAPTER 14

Treatment of the Cerebrovascular Complications of Hypertension

DIFFERENTIAL DIAGNOSIS OF CEREBROVASCULAR SYNDROMES ASSOCIATED WITH HYPERTENSION

The chief features of the six cerebrovascular lesions most commonly associated with hypertension are presented in Table 9. The practical differentiation of these syndromes is often difficult but since their treatment differs, an accurate diagnosis is important. In cerebral vasospasm, cerebral hemorrhage, and acute diffuse hypertensive encephalopathy, the blood pressure prior to the attack is usually very high. In cerebrovascular thrombosis as well as in the cerebrovascular insufficiency syndrome and in subarachnoid hemorrhage, systolic readings below 200 mm. Hg are commonly encountered.

Cerebral hemorrhage causes a massive neurologic deficit, usually a hemiplegia, which rapidly progresses into coma. The history commonly reveals a previous blood pressure consistently above 200 mm. Hg and often considerably higher than the usual value for the patient just before the episode. Headache is prominent in the early stages, and in most cases the spinal fluid shows the presence of many red blood cells. The hemorrhage causes an acute rise in cerebrospinal fluid pressure, which will lead to

Table 9. Differential Diagnosis and Early Treatment of Cerebrovascular Syndromes in Hypertension

Diagnosis	Blood pressure with attack	Neurologic signs	Special features	Early treatment: Lower BP?	Early treatment: Anticoagulant?
Cerebral vasospasm	Very high or recent acute rise	Focal	Transient attacks, spinal fluid normal	Yes	No
Cerebral hemorrhage	Same	Extensive focal or diffuse	Massive paralysis; blood in spinal fluid; pressure increased	No	No
Acute diffuse hypertensive encephalopathy	Same	Diffuse	Cerebrospinal fluid pressure usually elevated	Yes	No
Cerebral thrombosis	Not greatly elevated or no recent rise	Focal	Persistent neurologic deficit; spinal fluid normal	Yes?	No
Cerebrovascular insufficiency	Same	Focal	Recurrent brief attacks, spinal fluid normal	No	Yes
Subarachnoid hemorrhage	Normal or high (acute rise after onset)	Diffuse	Blood in spinal fluid, pressure increased	Yes	No

papilledema and retinal hemorrhages and exudates, together with a further elevation of the arterial pressure. In contrast to this picture, the onset of a less severe focal neurologic deficit with recovery of function within a few hours in a patient with a very high blood pressure usually indicates an episode of cerebrovascular spasm. Sometimes, instead of a focal disturbance, the patient with very greatly elevated blood pressure lapses into a state of mental confusion and disorientation This clinical syndrome has been identified by Fishberg (1954) as acute diffuse hypertensive encephalopathy. Cerebrospinal fluid pressure is usually elevated. Papilledema and advanced retinopathy are frequently apparent. Consistent reduction in the blood pressure over a 24- to 48-hour interval results in progressive improvement, and maintenance of this reduction may result in permanent beneficial effects. When mental confusion persists despite blood pressure reduction, the possibility of another lesion such as a subdural hematoma should be considered, as in the case history quoted on p. 61. Diffuse encephalopathy may also occur abruptly as the result of a rapid increase in intra-arterial pressure This form is seen characteristically in acute nephritis and toxemia of pregnancy.

In contrast are three lesions not directly related to very high blood pressure, which may occur with little rise in the blood pressure above usual levels. Cerebrovascular thrombosis is probably the most common Its effects vary from involvement of a small portion of the central nervous system to a gradually progressive hemiplegia. The onset is less explosive than that of the acute lesions described above. The pressure is not greatly elevated; it may be no higher than the individual's usual level. The spinal fluid is free of red blood cells and xanthochromia and is not under increased pressure. Finally, although the lesion may improve considerably in the first few weeks, a residual deficit usually remains When such neurologic episodes are repetitive and transient and can be related to postural, postprandial, or drug-induced reductions in blood pressure, the possibility must be considered that they are caused by cerebrovascular insufficiency. The history of this condition may resemble that obtained in cerebral vasospasm, with the notable difference that at the time of onset the blood pressure is not greatly elevated,

or at least no higher than usual for the patient. The insufficiency syndromes are associated with advanced arteriosclerosis and are rarely seen in the younger patient. Finally, one must consider the possibility of a spontaneous subarachnoid hemorrhage in the differential diagnosis of cerebrovascular lesions associated with hypertension. This event, which follows rupture of a congenital or acquired aneurysm, occurs with somewhat greater frequency in the hypertensive than in the normotensive patient. Perhaps increased intra-arterial pressure may induce aneurysmal dilation of "weak spots" in the cerebral circulation. It is not commonly preceded by great elevations of the arterial pressure. The diagnosis should be considered when loss of consciousness occurs suddenly without focal neurologic signs and in association with blood in the spinal fluid. An acute rise in cerebrospinal fluid pressure may rapidly produce papilledema with retinal hemorrhages and exudates and excite a reflex elevation of the arterial pressure, so that the clinical picture that develops may resemble malignant hypertension complicated by diffuse hypertensive encephalopathy. The appearance of blood in the cerebrospinal fluid may be the single differentiating characteristic.

The differential diagnosis presented in Table 9 is not accepted by all neurologists, but represents an attempt to reconcile differing viewpoints. There is, for example, considerable disagreement concerning the occurrence of cerebrovascular "spasm" in hypertension, particularly since the recent recognition of the frequency of vascular insufficiency syndromes. Since opposite recommendations for management of the blood pressure are made in these two conditions, some discussion of the possible mechanisms of transient focal neurologic syndromes in hypertensive patients is in order.

Certain authors have recently ascribed all such repetitive focal attacks to intermittent cerebrovascular insufficiency with or without recurrent cerebral embolization. This view is supported by the frequency of cerebral arteriosclerosis in such cases. Autopsy records have been quoted to show the frequency with which partial obstruction of a major artery to the brain is caused by an arteriosclerotic plaque or by organization into the artery wall of recurrent thrombosis. The result is to reduce the size of the lumen and to lower cerebral perfusion pressure. Superimposed on

this defect, a transient reduction in systemic blood pressure c the release of small emboli may serve to produce brief episodes c cerebral dysfunction from which complete recovery is possibl In the case described by Eastcott, Pickering and Rob (1954 systemic hypotension from paroxysmal tachycardia was the initi ating event.

Reasoning from the results of anticoagulant treatment, Millika (1955) believes that some episodes are caused by detachment o thrombi formed on arteriosclerotic plaques in the major cerebra arteries and their subsequent dissolution in the cerebral circula tion, since anticoagulant therapy prevents these episodes. Bot explanations may apply in certain cases. The common pathologi background, however, is extreme arteriosclerosis of large cerebra arteries. Thrombotic lesions in the carotid arteries explained 3 per cent of the cerebral accidents found at necropsy in a series o elderly persons examined by Fisher (1954), who routinely dis sected the bifurcation of the common carotid arteries, a procedur not part of the usual autopsy procedure. The syndrome might b expected to occur chiefly in the arteriosclerotic variety of hyper tension, although it is not impossible for it to occur in long-stand ing and severe established hypertensive disease. The typical his tory is of repeated focal episodes in the same or related cerebral areas, often followed by only partial recovery, so that there is a progressive and stepwise deterioration in neurological function. When the basilar artery is involved, symptoms are more diffuse and may take the form of dizzy spells, vomiting, or brief syncope. The pathologic counterpart has long been recognized in other large arterial systems, as for example in the syndrome of aortic thrombosis described by LeRiche, and in the occurrence of myocardial infarction as a result of closure of a distant coronary artery, as described by Schlesinger. It is often difficult to confirm the diagnosis of cerebrovascular insufficiency, since the narrowing may occur in an area not subject to direct examination Sometimes decreased carotid pulsations are felt in the neck or by peritonsillar palpation of the internal carotid artery. A difference in retinal artery pressures occasionally reveals carotid occlusion (Drew, 1951). Murmurs over one carotid or over the skull may be helpful (Myers, 1956) but these may also be heard in the absence of vascular disease. Brief pressure on the right or

left common carotid may demonstrate vascular insufficiency by causing an attack or altering the electroencephalogram (Gurdjian, 1957). Cerebral angiography is not without risk but is the only certain way to make the diagnosis. Perhaps the most *practical diagnostic method is to observe the effect of a trial of* anticoagulant therapy if the attacks have been occurring with considerable frequency.

Despite the current interest in the cerebrovascular insufficiency syndrome, one should not lose sight of the considerable theoretical and clinical evidence that in hypertension a lesion may occur that is best described as resulting from focal cerebrovascular spasm. It is common knowledge, from observation of the retinal arteries that a severe rise in blood pressure may be associated with brief retinal artery constriction of major degree that may be completely reversible. Furthermore, every neurosurgeon has observed at operation spastic contractions of the cerebral arteries. Finally, Byrom (1954) has photographed cerebrovascular spasm in the hypertensive rat through a plastic window implanted in the cranium. The focal constriction that occurred after production of renal hypertension was followed by an increase in vascular permeability, as detected by patchy staining of the cerebral hemispheres when trypan blue was injected into the arterial circulation. Neurologic deficits then appeared that corresponded to the areas of cerebrovascular occlusion. Sections taken during the development of the lesion revealed first a spastic contraction of a small arterial trunk, followed by localized cerebral edema. Then a thrombus formed in the narrowed vessel and an area of cerebral softening developed. While these later lesions were irreversible, it was possible to abolish early spastic contraction when the blood pressure was reduced by removing the clip from the renal artery. Byrom postulated that high intraluminal pressure leads to a reflex vasospasm. Further support for this theory comes from the experiments of Robert (1956), who, by ligating the carotid artery, totally protected from brain injury rats made hypertensive by desoxycorticosterone.

Clinical experience suggests that a comparable process occurs in the human hypertensive patient. The retinal artery constriction of severe hypertension is associated with areas of hemorrhage and exudate not unlike those seen in Byrom's photographs. Acute severe elevations in blood pressure frequently precede the

development of transient focal neurologic signs, and reduction in the blood pressure, if accomplished promptly enough, is associated with the disappearance of these signs. This sequence of events is contrary to that which would be expected if the episode were caused by cerebrovascular insufficiency. It has been possible to find several cases in our clinic records in which a sudden further rise in blood pressure in a hypertensive individual preceded by one-half to one hour the onset of a focal cerebrovascular attack, and when the blood pressure was reduced the lesion showed no further development. We believe the diagnosis of cerebrovascular spasm can be made and insufficiency excluded when the patient is in the younger age group, exhibits a blood pressure above 200/130 mm. Hg, and when an acute rise in blood pressure precedes or accompanies the accident and antihypertensive treatment improves rather than worsens the neurologic lesion.

TREATMENT OF CEREBROVASCULAR VASOSPASM

Cerebral vasospasm is the probable diagnosis in a young hypertensive patient with a severe or recent elevation of blood pressure above his usual value, particularly when such a focal cerebral episode is transient.

Reduction of the Blood Pressure

Antihypertensive treatment in this condition should be prompt and effective. If the episode is of recent onset and the patient is in the hospital under close observation, infusion of Arfonad or some other vasodilator agent is recommended (Appendix 5, p. 266). If the condition improves, or at least is no worse, when the blood pressure is reduced, a longer-acting drug such as parenteral hexamethonium or pentolinium should be given (Appendix 5, p. 272). If the diagnosis was correct and the duration of symptoms less than one hour, the neurologic findings should be relieved within one to two hours after the blood pressure has been reduced. The initial therapeutic objective is to lower the systolic blood pressure to a point midway between the starting value and 150 mm. Hg. The infusion of Arfonad is adjusted so that the blood pressure is held at this point. If improvement is noted, it may be presumed that the diagnosis was correct. If the patient gets no worse, the antihypertensive program should

be continued on the assumption that while the initial lesion may have passed into an irreversible thrombotic phase, further difficulty may be avoided. If the condition progresses, the diagnosis is probably wrong and the infusion should be stopped. If the attack occurs at home and it is impossible to maintain supervision of the blood pressure, parenteral reserpine, 5 mg., can be given intramuscularly. This procedure usually has a moderate depressor effect which will be sufficient to relieve the excess hypertension that may have set off the cerebral vasospasm. If reserpine is not available, sublingual nitroglycerine may be given. It should be taken in the upright posture, to obtain maximal hypotensive effects. If the experiments of Byrom in the rat apply to the problem of human cerebral vasospasm, the most important factor is the initiation of treatment before the cerebrovascular constriction has induced irreversible thrombosis. For this reason patients subject to such attacks should be warned in advance what to do and should carry vasodilators with them. For the same reason it will not be expected that all attacks of "vasospasm" will be reversible, particularly if treatment is delayed.

Cerebrovascular spasm may exist only in the initial phase of cerebral thrombosis. To prevent recurrence of spasm, antihypertensive treatment should be strictly regulated by recording the blood pressure in the home, and a near normal standing blood pressure should be achieved by the usual treatment methods (Appendix 7, p 278).

Other Forms of Treatment

The same measures that are used for an acute attack of cerebral thrombosis (p. 146) may be used in the early treatment of cerebrovascular spasm. Anticoagulant therapy is not recommended when the diagnosis of vasospasm is reasonably certain.

TREATMENT OF CEREBRAL HEMORRHAGE

Reduction of the Blood Pressure

While it is the impulse of most physicians to seek to lower the blood pressure in an acute attack of cerebral hemorrhage, a very limited experience with this condition gives no hope that such a

reduction will be beneficial in most cases. In the first place, it is probable that the bleeding will have stopped by the time the physician sees the patient. Furthermore, a reduction in blood pressure may disturb the relationship between intracranial and intra-arterial pressure and actually hasten death. Thus, in one case which was treated by the parenteral administration of a ganglion-blocking agent, a rather frightening period of apnea ensued when the blood pressure was brought to near normal levels. A spontaneous fall in blood pressure usually occurs not long after the onset of a massive intracerebral hemorrhage. On numerous occasions before antihypertensive drugs could be obtained or an infusion started, the blood pressure of patients under our observation has begun to fall, continued rapidly downward, and stabilized at low levels during the remainder of the patient's life. Therefore, as much as one would wish to do something in this grave emergency, it is probable that neither the classical methods of phlebotomy nor the modern methods of blood pressure reduction are of much value If it is decided to attempt nevertheless to lower the blood pressure, this should be done with great care and with the use of a short acting drug so that, if an adverse reaction occurs or hypotension develops spontaneously, the added effects of the drug will not be disastrous Therefore the method of choice in this situation would be to give an infusion of Arfonad (Appendix 5, p 266).

In no other aspect of the management of hypertension is the importance of prophylaxis worthy of more stress. Confronted with a massive cerebral hemorrhage, the physician is helpless. On the other hand, such an attack may almost certainly be prevented by insisting on strict blood pressure control in the severely hypertensive patient. If one elects not to attempt to reduce the blood pressure in a case of severe established hypertension, the risk of a sudden stroke is ever present. Often there are no specific warning signs of impending cerebral hemorrhage. All patients with severe hypertension are under constant threat from this disaster. The risk of the development of this lesion is the greatest argument for prophylactic reduction of the blood pressure in a patient without a demonstrable vascular complication. The other terminal events of hypertension can usually be foreseen in sufficient time to prevent or at least to postpone the fatal outcome,

but this is not the case with cerebral hemorrhage. Any one who has treated large numbers of hypertensive patients before and during the era when effective drugs were available will attest to the infrequency of cerebral hemorrhage in those patients whose blood pressure is well controlled. If further evidence were needed to support the impression that chronic lowering of the blood pressure, even in its present incomplete and frequently inadequate form, has an effect on the incidence of cerebral hemorrhage, the experience at the University of Michigan Hypertension Clinic can be cited. While a number of instances of fatal strokes are known to have occurred in patients unwilling or unable to maintain adequate control of their blood pressure with mecamylamine, only two instances of cerebral hemorrhage have been observed in patients attending the Hypertension Clinic who have had satisfactory reduction in blood pressure readings as recorded in the home. These two episodes have occurred at night in severely hypertensive subjects whose standing blood pressure was brought to a normal level but whose recumbent reading was little affected by medication. This further attests to the importance of cerebral arterial pressure elevation as a major factor in cerebral hemorrhage, and emphasizes that reduction of the orthostatic blood pressure alone will not guarantee complete immunity from cerebral hemorrhage.

In the rare instance of recovery from this complication, a major disability usually persists. What treatment for the blood pressure should be prescribed after the attack? Many factors must be considered. To complicate a severe neurologic disability such as hemiplegia or aphasia by superimposing the side effects of drug treatment appears to be unjustifiable in the average case. Furthermore, if patients are confined to bed, the beneficial effects of posture on the treatment cannot be utilized. If the patient is not bedridden, however, and the blood pressure remains greatly elevated, one should probably make some effort to reduce the pressure by whatever means is acceptable.

Other Forms of Treatment

It is obvious from the foregoing that the average case of massive intracranial hemorrhage pursues its predestined course without the physician being able to alter it substantially. The mor-

tality rate is high, and death usually occurs within the first day or two. If the patient survives this interval, he is likely to remain permanently paralyzed. In a very few instances the clot may enlarge and add to the deleterious effects by pressure on neighboring cerebral structures. If the clot is evacuated in time, residual damage may be less than if it is permitted to reabsorb spontaneously. The indications for such a surgical intervention are by no means clear, but among the prerequisites should be evidences of progressive deterioration, marked papilledema, changing pupillary size, evidence of shift of the pineal gland, compression of one of the ventricles, or of increasing intracranial pressure. In the more severe cases, evacuation of the clot may convert a moribund patient to a hopeless cerebral cripple. On the other hand, in the less severe types of hemorrhagic disease, the reduction in ultimate disability may be dramatic. Cerebral angiograms may be helpful in localizing the position of the expanding lesion. When there is such evidence, early evacuation of the clot is reported to improve the prognosis and may be performed without great risk (Guillaume, 1957). We have had little experience with this procedure, but the following case history indicates the possibility for benefit.

Case History

A 44-year-old man with known severe but asymptomatic hypertension secondary to chronic pyelonephritis was admitted to the University of Michigan Hospital after the abrupt onset of headache, vomiting, and left hemiplegia a few hours previously. The blood pressure readings in the Out-Patient Clinic had varied from 160/120 mm. Hg to 210/140 mm. in previous months. On admission, the patient was semicomatose and the neurologic findings were compatible with a massive left hemiplegia. There was bilateral papilledema without hemorrhages or exudates. The blood pressure was in excess of 300 mm Hg systolic and 180 mm. diastolic. Pulse was 108. The patient's condition gradually worsened in the next few days. Coma deepened, hyperactive reflexes and a positive Babinski sign appeared in both lower extremities. A paralysis of the left oculomotor nerve developed. A right subtemporal craniotomy was performed and a large intra-

cerebral clot was evacuated. In the first 24 hours after surgery there was no improvement. The blood pressure fell to 130/80 mm. Hg and periods of apnea appeared. Thereafter, gradual improvement set in. Within two weeks he was discharged from the hospital with only a mild residual left hemiparesis and a blood pressure of 170/110 mm. Hg. At the present time, two years later, he has complete use of his extremities and is back at work.

COMMENT. Confronted with a clear-cut diagnosis and a rapidly deteriorating condition, neurosurgical intervention appeared to have been lifesaving in this case. Of additional interest was the characteristic posthemorrhagic blood pressure rise which was relieved by the craniotomy.

TREATMENT OF ACUTE DIFFUSE HYPERTENSIVE ENCEPHALOPATHY

Differential Diagnosis

The diagnosis of acute diffuse hypertensive encephalopathy should be considered in all patients with severe or recently progressive hypertension who experience episodes of mental confusion or a reduction in general awareness. Uremia and the effects of rauwolfia drugs may lead to a condition similar to encephalopathy. Subarachnoid hemorrhage may cause loss of consciousness. Occasionally cerebrovascular arteriosclerosis presents a similar clinical picture, but in this case the diastolic blood pressure is not greatly elevated, or at least is not above the usual level for the patient.

When the blood pressure elevation is extremely rapid, as in toxemia of pregnancy or acute nephritis, diffuse encephalopathy usually is accompanied by cerebral edema and convulsions. Unconsciousness with convulsions in a hypertensive patient may follow many years after a hypertensive cerebral accident, and may also follow severe hypotensive episodes while the patient is under treatment with antihypertensive drugs (see Case History, p. 163). Mention has also been made of the gradual loss of consciousness that may follow the development of a subdural hematoma in a patient who also has hypertension (see Case

History, p. 61). Deepening confusion and coma in such a patient can easily be mistaken for hypertensive encephalopathy, particularly if there is no history of head injury.

Reduction of the Blood Pressure

Prompt reduction of the blood pressure is essential. It is reasonable to follow the rule of maintaining a systolic blood pressure midway between the starting value and 150 mm. Hg. The treatment of choice in an emergency is to give Arfonad or hexamethonium intravenously (Appendix 5, p. 266). When the necessity for blood pressure reduction is less urgent, reserpine or hexamethonium may be given intramuscularly (Appendix 5, p. 272). Protoveratrine is also an excellent and rapidly acting agent for this purpose. The technique of administration is described in Appendix 5, p. 268. If a blood pressure reduction is maintained for a continuous period of 24 to 48 hours without clinical improvement, either an erroneous diagnosis has been made or the lesion has progressed to the point of permanent and irreversible brain damage. As a general rule, the longer the duration of encephalopathy before treatment, the longer the period of blood pressure reduction necessary to produce improvement.

After relief of the acute episode, long-term treatment of the blood pressure must be energetic to prevent a recurrence. For this purpose ganglion-blocking drugs or sympathectomy supplemented by chlorothiazide will usually be necessary. Strict supervision of the daily blood pressure is advisable, as in other regimens for the long-term control of hypertensive disease (Appendix 7, p. 278).

Other Forms of Treatment of Diffuse Hypertensive Encephalopathy

Whether this syndrome is associated with toxemia of pregnancy, renal excretory failure as in acute nephritis, or hypertensive disease, blood pressure reduction is usually the most effective single measure that can be used. Sedative agents are sometimes helpful. Five hundred milligrams of chlorothiazide intravenously has been recommended. Magnesium sulfate, 2 ml. of a 50 per cent solution, intramuscularly every 4 hours, is reasonably successful in acute nephritis in children but less so in the adult. It is contraindicated when anuria is present.

TREATMENT OF CEREBROVASCULAR THROMBOSIS

Reduction of the Blood Pressure

Theoretically, in cases of acute cerebrovascular thrombosis the blood pressure should not be reduced, for fear of extending the infarction. In the acute phase, however, the diagnosis is difficult to make. One diagnostic criterion for thrombosis is that the neurologic finding does not promptly regress. Since this cannot be known at the time of onset, the possibility of a cerebral vasospastic episode cannot be excluded. The following program is therefore recommended. If the blood pressure at the time of the attack exceeds 230/130 mm. Hg and the onset was abrupt, a vasospastic element may be involved and a cautious effort is made to reduce the blood pressure, particularly if the patient is seen within a few hours after the onset of the attack. Reduction of a very high blood pressure in cases subsequently recognized as thrombosis has rarely seemed to extend the lesion, despite the theoretical possibility that this might happen. If the systolic blood pressure is below 200 mm. Hg at the time the patient is seen, and the onset of the attack is gradual, or if the patient is first examined 6 to 8 hours after the appearance of the first symptom and has shown no sign of improvement, no blood pressure reduction is attempted during this phase of the illness.

This is clearly an uncertain field for the use of potent depressor drugs, but if one attempts to lower the blood pressure, the agent of choice must be a short-acting one so that, if the neurologic defect appears to increase, the blood pressure may be allowed to rise without delay. Furthermore, the degree of blood pressure reduction should be limited, to avoid any risk of extending the thrombosis. If the goal in reducing the recumbent systolic blood pressure is established at one half the difference between the initial reading and 150 mm. Hg, a cerebral episode resulting from excessive vasospasm will be relieved, while the risk of extension of thrombosis by such treatment is relatively minor. Parenteral reserpine may be tried in this situation, although the sedative effects of the drug may cause some difficulty in detecting whether the original lesion has improved. Precise

and transient blood pressure control can be better achieved by intravenous Arfonad (Appendix 5, p. 266). If the reduced blood pressure is well tolerated, ganglion-blocking agents or reserpine can be used for more prolonged effects.

Once the neurologic lesion is stabilized in a case of severe hypertension, questions arise concerning prolonged reduction of the blood pressure by antihypertensive drugs. Does reduction in pressure from severely elevated levels reduce the likelihood of recurrence at a later date? If on such a program severe hypotension occurs occasionally, is there added risk of precipitating a second cerebral thrombosis? The answer to the first question must be incomplete in the present state of our knowledge. The following arguments, however, favor efforts to reduce the pressure. In a young person, cerebral thrombosis is rarely seen in the absence of sustained arterial hypertension; elevated blood pressure then must play some role in the pathogenesis of the lesion. Sustained reduction of the blood pressure may at least prevent the further development of atherogenesis of the cerebral vessels and thus reduce the likelihood of recurrences. Furthermore, if cerebral spasm is initiated by high cerebral arterial pressures and if this process precedes thrombosis as suggested by Byrom's studies (1954), then an antihypertensive program should be helpful. Statistical evidence that blood pressure reduction has some protective influence on the frequency of subsequent cerebrovascular deaths follows from the studies of Pierson and Hoobler (1957), who reviewed the prognosis for recurrence of cerebrovascular episodes in patients with an initial cerebrovascular lesion but without other major complications of hypertension. They found that the recurrence rate for fatal cerebrovascular accidents, type unspecified, was approximately 30 per cent in 5 years in 131 patients whose blood pressure was either untreated or uninfluenced by sympathectomy, whereas in a comparable series with partial blood pressure reduction following sympathectomy the recurrence rate in 5 years was only 5 per cent. Although the differences were statistically significant, the number of cases was small and the ultimate cause of death, whether hemorrhage or thrombosis in the cerebral circulation, was not known. The study did provide support, however, for the view-

point that reduction of blood pressure in a patient who has had a focal cerebral attack *lessens the possibility of death from* cerebrovascular disease.

The second question to be considered is whether there is any significant risk of precipitating a second attack of thrombosis if, as so often happens, therapy is associated with occasional hypotensive episodes. When too great a reduction in blood pressure is accomplished immediately after cerebrovascular thrombosis, a brief worsening of neurologic signs has been occasionally observed. The situation is perhaps akin to the precipitation of angina pectoris by a too rapid therapeutic reduction in blood pressure. When antihypertensive treatment is more gradually applied, an asymptomatic reduction to levels originally not well tolerated may be achieved. At such a lower level it is then to be hoped that the frequency of recurrences will be reduced. The more the initial blood pressure is elevated, the greater is the possible secondary benefit from control of the hypertension. Not only is the patient protected against a second cerebrovascular attack but he is also less likely to succumb to cardiac or renal lesions of hypertension. In view of these considerations it is recommended that after cerebrovascular thrombosis has occurred in a patient with severe or moderately severe hypertension (systolic blood pressure above 200 mm. Hg) antihypertensive therapy should be started as soon as the neurologic defect has stabilized. Reserpine, chlorothiazide, and a ganglion-blocking agent if necessary, are prescribed and the blood pressure is lowered very gradually, taking several weeks to reach the desired systolic range of 140 to 150 mm. Hg in the standing position. Such reduction should then be maintained indefinitely, with proper monitoring of the blood pressure by the patient in the home (Appendix 7, p 278). Should anticoagulants also be used (see below) very strict control of the blood pressure is mandatory.

Other Forms of Treatment

The variety of treatments recommended for the acute attack attest to their uncertain value and the unpredictable natural course of the disease. Insufficient knowledge of the pathologic physiology of the cerebral circulation in these patients adds to our sense of inadequacy in dealing with this serious complica-

tion. If a vasospastic phenomenon initiates the lesion or is a factor in increasing the area of cerebral ischemia, then once a thrombus is formed, agents that dilate cerebral arterial smooth muscle should be effective. Judging from the experience reported by Byrom in studies on the rat, the earlier vasodilator drugs are used the more likely they are to prevent an irreversible lesion. Since the cerebral attack rarely occurs under the physician's observation, it is perhaps advisable to have some vasodilator immediately available to the patient. Among those which have been recommended are sublingual nitroglycerin, pearls of amyl nitrite, or a plastic bag carried with the patient that may permit him by rebreathing to achieve the cerebrovascular dilation that follows increased carbon dioxide retention in the blood. In a very limited experience we have failed to observe much relief from transient cerebral attacks by the early use of these procedures.

Among the immediate measures available to the physician when he first sees a patient with an early cerebral thrombosis are the intravenous administration of papaverine 100 mg. over a period of 30 minutes; the use of 500 mg. of aminophylline intravenously followed by a slow infusion of 500 to 1000 mg. over 4 to 6 hours; administration of 5 per cent carbon dioxide in room air through an intranasal catheter, and block of the stellate ganglion. Despite theoretical indications for some of these procedures, brief experience in the Hypertension Clinic plus a review of the literature yields little evidence that improvement under such treatment exceeds the natural rate of recovery in this disorder.

The initiating lesion in cerebral thrombosis is probably the coagulation of blood around an atherosclerotic plaque in a diseased cerebral artery. Anticoagulant therapy should theoretically be as helpful in preventing a recurrence of cerebral thrombosis as it is in preventing recurrences of myocardial infarction. However, the fear that some patients receiving anticoagulant drugs may succumb to cerebral hemorrhage, together with the uncertainty of distinguishing between hemorrhage and thrombosis in some cases, has led to considerable caution in applying such treatment to patients with a history of cerebrovascular disease. Wright and his collaborators and Millikan have been using this treatment regimen in patients with moderate hypertension for

several years without a noticeable increase in the incidence of cerebrovascular hemorrhage so long as the systolic blood pressure has generally been kept below 200 mm. Hg. Whether the risk of hemorrhage in prolonged anticoagulant treatment is less than the risk of recurrence of cerebral thrombosis is at present unknown. Until further information is available, anticoagulant treatment should be left for experimental study, particularly when there is concomitant severe hypertension.

Cerebral thrombosis is also a frequent complication of polycythemia vera, because of the increased viscosity of the blood and the elevated platelet count in this condition. For this reason, a high value for the hematocrit in patients with hypertension and cerebral thrombosis should be verified, and if polycythemia is found, treatment to reduce the hematocrit should be initiated.

Patients who exhibit a persisting neurologic disability should be examined by a competent physiotherapist as soon as possible after the accident. A great deal can be accomplished by early physical therapy and retraining exercises to minimize the ultimate disability and to give the patient a more optimistic outlook concerning his future.

TREATMENT OF CEREBROVASCULAR INSUFFICIENCY

Reduction of the Blood Pressure

In the vascular insufficiency syndromes, blood pressure is not greatly elevated, or is characterized by a high systolic and a low diastolic reading. When the basilar artery is involved, the symptoms are usually nonspecific and may consist simply of attacks of dizziness or nausea often associated with the upright posture, in which position vertebral artery pressure may be reduced below the critical level for cerebral perfusion. When the carotid arteries are involved in the insufficiency syndrome, recurrent unilateral focal episodes may occur under conditions of lowered pressure. Once this syndrome is suspected or seriously considered, antihypertensive treatment is contraindicated. Since in any event the pressure is usually not greatly elevated, there is little need for potent antihypertensive drugs. If the patient is to take anticoagulant drugs, however, some control of the blood

pressure with milder agents such as reserpine and chlorothiazide may be advisable in long-term treatment.

Other Forms of Treatment

Millikan has demonstrated the dramatic effectiveness of anticoagulant therapy for this particular symptom-complex. In his first report (1955) he described the abrupt cessation of transient episodes that had been recurring for weeks or months before institution of an anticoagulant regimen. It would be difficult to explain the effectiveness of this treatment if the insufficiency syndrome were simply the result of systemic hypotension superimposed on a cerebral artery narrowed by partial thrombotic occlusion. Millikan has reasoned that the recurrent focal neurologic episodes represent temporary cerebral ischemia, which follows detachment of minute emboli from thrombi that keep forming about arteriosclerotic plaques in the larger cerebral arteries. He postulates that the usual fibrinolysins in blood dissolve these emboli so quickly that normal function is promptly restored to the cerebral area involved. In his view, anticoagulants prevent the initial formation of the thrombi on the arteriosclerotic lesion; hence, embolism and transient neurologic symptoms no longer occur. This seems the only reasonable explanation for the prompt cessation of attacks a few hours after a satisfactory anticoagulant effect is obtained. The following case history from the Hypertension Clinic records illustrates the effectiveness of this form of treatment.

Case History

A 67-year-old retired contractor was admitted to the University Hospital in December, 1955, with the complaint that for 2 weeks he had experienced recurrent brief episodes of numbness and weakness of the left arm, drooping of the left side of the face, dysphagia, and confusion. Sixteen years before, he had suffered a right hemiplegia with almost complete recovery. Two years later he had undergone a sympathectomy for hypertension, with a reduction in blood pressure from 200/120 mm. Hg to 150/90 mm. The lower readings had persisted from the time of operation almost to the present. On admission the blood pressure

was 180/100 mm. Hg. The remainder of the physical examination was not remarkable except for signs of generalized arteriosclerosis. The neurological examination between attacks showed no defects. The routine laboratory tests were within normal limits. While under observation in the hospital he experienced from one to four attacks daily, lasting from one to five minutes and marked by slurred speech, weakness, and numbness of the fingers of the left hand. These episodes were not associated with changes in posture or blood pressure. Sublingual nitroglycerin relieved the attacks perhaps more rapidly than spontaneous recovery. Inhalation of 5 per cent carbon dioxide had no apparent effect on the duration of the attacks. As soon as anticoagulant therapy was started the episodes stopped abruptly and have not recurred in the subsequent three years of treatment.

COMMENT. This case closely resembles those described by Millikan. The relative inefficacy of vasodilators in acute attacks and the remarkable effectiveness of anticoagulant therapy are noteworthy. The importance of suspecting the diagnosis in such cases is obvious. Prompt response to anticoagulant treatment may confirm the suspected diagnosis in doubtful cases.

In chronic cerebrovascular insufficiency where the diagnosis is certain and a permanent defect has occurred or is imminent, the use of stellate ganglionectomy has been recommended. Sometimes it has been possible, as in Eastcott's case (1954), to remove the thrombosed segment, which commonly occurs at the bifurcation of the internal and external carotid branches, and to perform an end-to-end anastomosis. This surgical approach to obstruction of major cerebral arteries is likely to prove most profitable and, at least for the carotid artery syndromes, it will undoubtedly replace other forms of treatment when proper surgical techniques have been developed. To localize the obstruction, diagnostic procedures will have to be improved. At present the only certain diagnostic technique is cerebral arteriography, which carries a considerable risk. Demonstration of a reduction in retinal artery pressure on one side has been advocated as a diagnostic method, but in many cases collateral flow across the circle of Willis permits the pressure in both retinal arteries to be equal despite a complete block in one internal carotid artery. Intermittent pressure on the contralateral carotid artery may evoke

transient syncope. Measurement of electroencephalographic changes during such occlusions may help to render the findings more objective.

Until more exact diagnostic methods have been achieved, the internist should consider every case of a transient recurrent cerebral episode as a potential example of vascular insufficiency, particularly when the systolic blood pressure is below 200 mm. Hg. Since the symptoms of the attacks closely resemble those created by cerebral vasospasm and treatment of the two conditions is diametrically opposed, considerable attention should be placed on the differential diagnosis. When no diagnosis can be made, a trial of anticoagulants may be warranted.

TREATMENT OF SUBARACHNOID HEMORRHAGE

Reduction of the Blood Pressure

The history of subarachnoid hemorrhage suggests that episodes of bleeding before the fatal termination may not be massive. Since the production of controlled hypotension may reduce the tendency to arterial bleeding in the cerebral circulation, a continuous reduction in blood pressure during and immediately following an attack may prevent a further and fatal hemorrhage. The question arises as to the most effective way to lower the blood pressure and to maintain such a reduction for several days in the mild or moderately severely hypertensive patient who has sustained a subarachnoid hemorrhage. Ideally one should maintain the systolic blood pressure for several days at 100 to 120 mm Hg, a point barely sufficient to maintain adequate urine flow. This may be achieved by parenteral reserpine plus the continuous intravenous infusion of Arfonad or sodium nitroprusside (Appendix 5, p. 266). Ganglion-blocking agents such as hexamethonium, pentolinium, chlorisondamine, or trimethidinium, in combination with chlorothiazide, may be given by frequent injections as indicated in Appendix 5, p 272 When attempts are made to reduce blood pressure to subnormal levels by injection or infusion of depressor drugs, the possibility of oliguria, anuria, and fluid retention must always be considered. A careful record of fluid intake and output should be maintained from the start, and the patient should be attended by a special nurse to super-

vise control of the blood pressure. Infusions should be given in as small a volume of fluid as possible. All the recommended drugs, except nitroprusside, may provoke paralytic ileus. Daily enemas are often necessary, but when the patient becomes lucid, care should be taken to avoid straining on a bedpan or attempting to void, since this may precipitate recurrent intracranial bleeding. The common practice of keeping these patients strictly recumbent does not appear to have a rational basis. To produce the lowest possible cerebral arterial pressure and thus to prevent a further vascular leak, the head-up position in bed would seem preferable, particularly in taking advantage of the orthostatic effects of a ganglion-blocking agent. It is possible that mechanical devices to lower the blood pressure as described by Restall and Smirk (1952) may come into use to add to the effectiveness of this difficult program.

When a period of two or three days without a recurrence of bleeding has passed, the use of continuous infusions or injections should be gradually relaxed on the assumption that the risk of bleeding has been reduced. The most effective regimen possible is then prescribed for controlling the blood pressure. It should include the liberal use of rauwolfia alkaloids given in combination with chlorothiazide.

The long-term management of the blood pressure of a hypertensive patient who has survived a subarachnoid hemorrhage must now be considered. Since this is a complication directly related to the height of the blood pressure, every effort must be made to achieve effective prophylaxis by using chlorothiazide, reserpine, mecamylamine, or sympathectomy (Peet, 1949) to keep the standing systolic blood pressure below 150 mm. Hg. Fortunately, hypertension associated with this complication is usually mild and the blood pressure lower than at the time of the intracranial bleeding so that the problem of its control is not so difficult in the later phases of management.

Other Forms of Treatment

It is not within the scope of this text to review the highly controversial forms of treatment that may be useful in this condition. The question of the indications for and against cerebral angiograms, the timing of this procedure, and the choice of operative

intervention are matters of concern for the consulting neurosurgeon.

CEREBRAL SYMPTOMS CAUSED BY TREATMENT

GENERAL CONSIDERATIONS

Too great reductions in blood pressure by any antihypertensive agent may restore the symptoms and the signs of a recent cerebrovascular episode. In the unstable stage that follows a hypertensive cerebral accident, it is advisable not to depress the blood pressure too quickly. The general rule is to seek an initial reduction no more than halfway from starting levels to the upper limits of normal. A cerebral side effect of too vigorous therapy that is common to all ganglion-blocking agents should be mentioned here because it occasionally produces confusion in the mind of the internist. This consists in the occurrence of postural syncope. Most patients who have been taking ganglion-blocking agents for some time learn to recognize the premonitory signs of acute cerebral hypotension. They recognize the dizziness, dimming of vision, and mental confusion, and learn to sit or lie down promptly to compensate. Sometimes, however, the episode of blackout occurs without warning This is more likely to occur just after the patient first gets up in the morning or when physical exercise or a heavy meal diverts blood away from the cerebral circulation. The episodes may come on so swiftly that the patient falls to the ground without warning and first learns of his attack when he recovers consciousness. Fortunately, since assumption of the recumbent position rapidly corrects the cerebral hypoxia, recovery from these episodes is usually rapid. It is important that all patients under therapy with ganglion-blocking drugs be aware of this tendency and make every effort to protect themselves against possible syncope in a position where it will be impossible for them to assume the recumbent posture. One thinks of telephone booths and toilets as places where serious accidents might conceivably occur. Men under treatment with mecamylamine often experience blackout spells while shaving It would perhaps be advisable for a patient taking these drugs to carry a card that would give instructions about what should be done in the event of an attack. Superficially these attacks resemble severe enceph-

alopathy; or their onset may call to mind a cerebral hemorrhage, particularly when the blood pressure is taken in recumbency and found greatly elevated. Knowledge of the blood pressure at the time and in the position of the attack will help in the differentiation. Such hypotensive episodes never occur when the patient is recumbent and are always promptly relieved by the head-down position. Although these attacks are rarely observed while the patient is sitting, there is a slight theoretical risk in driving a motor vehicle. Although no serious consequences in our experience have followed driving a car under the influence of a ganglion-blocking agent, the patient should not engage in such occupations as operating a crane or an elevator or driving a bus, where sudden syncope might endanger other people.

The cerebral effects of rauwolfia alkaloids are, of course, well known. When these agents are given in large parenteral doses to depress the blood pressure, mental confusion and reduced awareness are expected side effects. If it is really important to follow closely the level of awareness in a cerebral emergency, reserpine should not be used because, like barbiturates and morphine, it may mask the underlying features of the disease. The usefulness of this drug in a hypertensive emergency, however, often takes precedence over any cerebral side effects. The physician must, therefore, decide whether he is willing to trade the ability to assess his patient's mental state for a period of easy, relatively safe, and modest control of the blood pressure. Rauwolfia in large doses may reproduce the tremor and rigidity of Parkinson's disease. Presumably no irreversible damage is created, and if the rauwolfia alkaloid has been effective, it should not be discontinued because of such a side effect until such time as this may be done with safety. In patients with hypertension and Parkinsonism, moderate doses of reserpine have not been known to aggravate the tremor.

Treatment with hydralazine occasionally precipitates nausea, vomiting, and an agonizing diffuse headache severe enough to suggest an impending cerebral hemorrhage. Symptoms may continue for 24 to 36 hours after withdrawal of hydralazine and are sometimes reactivated by small doses of this drug. The mechanism of this reaction is not known.

A peculiar confusional state following prolonged mecamyla-

mine administration has been described (Perry, 1957a). It is associated with choreiform movements and may occur in patients with renal failure or cerebrovascular disease who have been taking mecamylamine. The finding appears usually after lengthy periods of treatment and is commonly reversible some days to weeks after withdrawal of the medication In the Hypertension Clinic only two such cases have been seen, despite considerable experience with mecamylamine (Cottier, 1957). In each case the syndrome slowly improved after treatment was stopped. The tremor usually begins as clumsiness, progresses to a continuous purposeless choreo-athetosis that involves the arms and to a lesser extent the legs so that jumping, twitching, and writhing movements occur intermittently even while the patient is at rest. The ability to walk is often first to be affected. In one instance it was assumed that the patient had had a cerebral thrombosis until careful examination revealed an early form of mecamylamine tremor. It has been postulated that, since mecamylamine has a volume of distribution greater than extracellular fluid, it gradually penetrates into nerve cells, particularly when renal excretory failure favors retention of the drug (Schneckloth, 1956). A confusional state is sometimes associated with the tremor but is usually less prominent Recently a patient who had been admitted to our hospital with the diagnosis of manic psychosis, was shown to be suffering from mecamylamine intoxication.

SUMMARY

Six cerebrovascular syndromes are recognized in which antihypertensive drugs are recommended for treatment or prophylaxis. They include cerebral hemorrhage, acute focal cerebral vasospasm, acute diffuse hypertensive encephalopathy, cerebral thrombosis, cerebrovascular insufficiency, and subarachnoid hemorrhage. The recognition and treatment of the acute attacks is described; blood pressure reduction is advocated in the early treatment of all these conditions except hemorrhage, thrombosis, and the insufficiency syndrome Cerebrovascular insufficiency is described and differentiated from cerebrovascular spasm.

CHAPTER 15

Treatment of Hypertension Associated With Renal Complications

EFFECT OF PROLONGED BLOOD PRESSURE REDUCTION ON RENAL EXCRETORY INSUFFICIENCY

Since renal failure develops very slowly in the average case of hypertension, it should be possible by control of the blood pressure to prevent or arrest the development of this lesion if it is truly blood-pressure-dependent. Recent observations in both laboratory and clinic support the view that reduction of the pressure will arrest the progress of renal arteriosclerosis. In the rat made hypertensive by clamping one renal artery, the deterioration of the renal vasculature so evident in the contralateral unprotected kidney is not observed in the clipped kidney with reduced arterial perfusion pressure (Byrom, 1949). The following case history illustrates that further deterioration of renal function can be arrested when the blood pressure is substantially reduced.

Case History

A 42-year-old woman was admitted to the University gan Hospital in 1949 with a 5-months' history of heada current dizzy spells, and progressive blurring of vision. time her blood pressure was 250/155 mm. Hg. The retina s

hemorrhages, exudates, and papilledema; no other abnormalities were found. The urine was free of albumin or formed elements. Renal plasma flow, measured by para-aminohippurate clearance, was 225 ml. per minute, or about one third of the normal value. The glomerular filtration rate (inulin clearance) averaged 66 ml. per minute, which represents one half of normal function. Supradiaphragmmatic splanchnicectomy was carried out, and this resulted in a prompt and sustained blood pressure reduction to upper normal levels. These levels were maintained, according to records of follow-up visits in our clinic, for 4 years after the operation. At that time the renal plasma flow and glomerular filtration rate were again measured and found to be 180 and 54 ml. per minute respectively. The patient was entirely free of headaches, dizziness, and visual disturbances The physical examination was normal including the blood pressure reading but there were some areas of focal vasoconstriction in the retinal vessels.

COMMENT. A considerable degree of renal vascular disease had already occurred in this patient with malignant hypertension, and the disease would undoubtedly have led to uremia and death if a surgically induced reduction in blood pressure had not been accomplished. Despite the patient's normal blood pressure and good health after the operation, precise renal function measurements revealed no improvement. The conclusion is that vascular disease in the kidneys may be arrested by lowering the blood pressure but that restoration of normotension cannot be expected to restore normal function to kidneys seriously damaged by previous vascular disease.

Such experiences indicate that high pressure within the renal arterial system does produce or accelerate renal vascular disease. Despite the above experience, it is possible to find some instances of renal functional improvement after reduction in blood pressure. The case reported by Imber (1955) demonstrated that normal function may be restored in a kidney seriously affected by hypertensive disease when the blood pressure is reduced by removal of the contralateral ischemic kidney. In a careful study of the therapeutic effects of ganglion-blocking agents in chronic severe hypertension with renal impairment, Corcoran (1955a) and Moyer (1958) have both demonstrated gradual but definite

renal functional improvement after prolonged blood pressure reduction. From these studies it may be concluded that reduction of the blood pressure will prevent further renal deterioration *and may in a few instances lead to improvement of renal function after considerable time has elapsed.*

MANAGEMENT OF BLOOD PRESSURE IN RENAL INSUFFICIENCY

In view of these considerations it follows that rigorous control of the blood pressure in established hypertension is the best way to prevent *renal deterioration. This is particularly important in* the patient with established hypertension who shows signs of renal involvement such as persistent albuminuria, recurrent hematuria, or progressive reduction in phenolsulphonthalein excretion or whose renal function has already fallen to less than 50 per cent of normal as judged by the PSP excretion test. Treatment may not be mandatory to prevent a renal complication in the presence of lesser degrees of impairment of renal function. However, *prophylactic treatment is more likely to be successful* and requires less stringent control of the blood pressure when an adequate renal reserve is present. For this reason alone, some reduction of the blood pressure is probably advisable in most patients with severe established hypertension, even in the absence of an apparent renal complication.

Many hypertensive patients are first seen by the internist at a time when the *nonprotein nitrogen varies between 45 and 100* mg. per cent. These individuals require meticulous care in the management of their blood pressure. The first step is to correct all possible causes for prerenal azotemia. Adequate hydration should be assured by intravenous fluid administration when necessary. Congestive heart failure should be treated as effectively as possible, including the use of digitalis and diuretics. Protein intake should be reduced *to 40 Gm. or less daily.* Some indicator of renal excretory failure (nonprotein nitrogen, blood urea nitrogen, or serum creatinine) should be utilized to judge the effects of treatment in the azotemic patient. Then blood pressure reduction is commenced, using reserpine and a ganglion-blocking agent with a goal of maintaining a blood pressure reduction ap-

proximately midway between the patient's high level and a normal value. Chlorothiazide may also be used but must be given carefully, since it may aggravate the azotemia. When the pressure has been stabilized at the lower level, renal excretory function is re-evaluated by determining the blood level of the chosen indicator. If there has been no significant rise in this index, further blood pressure reduction may be induced until normal or near normal levels have been reached, at least in the orthostatic position. If, on the other hand, a rise in blood urea nitrogen or other renal functional index occurs, the reduction previously secured may be cautiously maintained for a while, since in patients with this degree of renal insufficiency, temporary increases in azotemia are almost inevitable following significant blood pressure reduction. After a week or so the kidneys seem to readjust to the reduced blood pressure, as evidenced by a return of the indicator substance to pretreatment levels, and a further reduction may then be attempted However, the renal response must be carefully followed. By this method, it may be possible in from a few weeks to several months to achieve a blood pressure reduction to normal without a significant rise in the nonprotein nitrogen or other index of renal failure. If the patient continues to co-operate and if no infection or other protein catabolic load is added, the initial degree of azotemia may very slowly fall in the succeeding months. If severe damage prevents the restoration of renal functional capacity, it is to be expected that such a degree of blood pressure reduction will at least protect against concurrent danger from the cerebral complications of hypertensive disease.

Case History

A 54-year-old colored man was admitted to the University Hospital in 1953 with the complaint of high blood pressure, blurred vision, and a "thumping of the heart" for one year. No record of previous renal disease could be obtained. The blood pressure was 226/146 mm. Hg. The fundi showed only arteriosclerotic vascular changes. There was considerable cardiac enlargement with prominent suprasternal pulsation, but no signs of congestive failure were evident. Urinalysis revealed 1-plus al-

buminuria and normal sediment. Serum creatinine was 3.4 mg. per cent and the nonprotein nitrogen 67 mg. per cent; both values were confirmed on several occasions when the patient was well hydrated. Because it was thought the patient was not sufficiently intelligent to co-operate and for fear the azotemia would worsen, ganglion-blocking drugs were not prescribed and the hypertension persisted during the next few months. He then attended another clinic where pentolinium, 100 mg. 4 times daily, was prescribed and he was taught to record his own blood pressure. He returned one month later with a reduction of blood pressure in the standing position to 140/92 mm. Hg and a recumbent reading of 207/131 mm. Hg. He has maintained good control of the blood pressure during the subsequent 3 years. At present his usual reading is 120/88 mm Hg standing and 180/118 mm. recumbent. The dose of pentolinium is now 50 mg. 3 times daily and 100 mg. at bedtime. His nonprotein nitrogen remains at 66 mg. per cent and the urine shows only slight albuminuria. He has been free of symptoms except on one occasion when he fell to the ground and was thought to have had a stroke, since he seemed to have lost consciousness, and his blood pressure was greatly elevated. On lowering the head and raising the feet, consciousness rapidly returned and it was later demonstrated that while his recumbent pressure was very high his upright blood pressure had fallen to levels consistent with the production of syncope. Moderate constipation and dryness of the mouth have been the only other side effects of treatment; these symptoms have been relieved recently by the addition of chlorothiazide 500 mg. twice daily to the regimen and with a concomitant reduction in pentolinium requirement to 125 mg. daily.

COMMENT. Because of our underestimation of the patient's capacities, ganglion-blocking agents and instruction in the technique of blood pressure taking were omitted in the management of this severely hypertensive patient. It was further believed at that time that blood pressure reduction would aggravate the azotemia. This treatment was initiated in another clinic, however, and it was proved that we had underestimated the probability of prolonged survival with azotemia. While he still has a

marked orthostatic blood pressure gradient, the recumbent readings have gradually fallen and the dose of the drug has been reduced to a point of minimal side effects, with the aid of concomitant treatment with chlorothiazide. The attack of postural syncope came on without warning, but because it was possible to obtain blood pressure readings at the time of the episode, the diagnosis of acute hypertensive encephalopathy could be excluded.

If the nonprotein nitrogen exceeds 100 mg per cent and the toxic signs of uremia are present, the hypertensive patient may well be considered in such a serious condition that treatment will inevitably be unsuccessful and will produce only the unpleasant side effects associated with the antihypertensive medication. If such a degree of azotemia is not accompanied by toxic symptoms, however, reduction of the blood pressure may still be effective in prolonging life. In such cases, a cautious trial of blood pressure reduction may meet with partial success.

EFFECT OF BLOOD PRESSURE REDUCTION ON THE URINARY FINDINGS

An index of good management of the hypertension is the response of albuminuria to treatment. When this abnormal finding is caused by the hypertension, good control of the blood pressure usually leads to complete disappearance or marked reduction in the proteinuria. When such improvement is not observed after what appears to be a good response of the blood pressure to treatment, it may be surmised either that the albuminuria is the result of an irreversible renal lesion, as in the case of primary renal disease, or that more effective antihypertensive therapy is necessary.

Gross hematuria may suddenly appear in patients with hypertension, either as a result of a ruptured vessel in the ureter, bladder, or urethra, or following an acute renal vascular lesion. In the former instances, the red blood cells are strikingly free of associated urinary abnormalities. In the latter case, the hematuria represents an ominous phase in the course of malignant hypertension and is usually accompanied by red blood cell casts and a

rapid deterioration of renal function. In both instances, severe hypertension is usually present and more effective reduction of the blood pressure is indicated.

CHOICE OF DRUGS FOR BLOOD PRESSURE REDUCTION

In order to protect remaining renal function from deterioration a considerable reduction in the blood pressure must be accomplished. Reserpine is usually not adequate for this purpose and a ganglion-blocking agent combined with chlorothiazide is necessary. Although mecamylamine is still the most useful ganglion-blocking drug, a gross tremor may develop after prolonged use of this agent when renal function is greatly impaired. This unpleasant reaction is slow to improve but not permanently harmful (Appendix 7, p. 281). If the drug is prescribed in the azotemic patient, he should be warned to report promptly any evidence of mental confusion or motor inco-ordination. If one wishes to avoid this complication entirely, chlorisondamine, pentolinium, or trimethidinium may be substituted. When renal excretory function is greatly impaired, the hypertensive patient experiences a prolonged blood pressure reduction with much smaller doses of these drugs than are usually employed.* He may also find that two small doses spaced 12 hours apart each day are sufficient for good control of the hypertension. When the constipating effects of parasympathetic blockade are particularly severe, some relief may be obtained by the administration by the parenteral route of $\frac{1}{10}$ to $\frac{1}{20}$ the usual oral dose of the ganglion-blocking agent once or twice daily. Trimethidinium because of less gastrointestinal side effects may be the drug of choice in these circumstances, but an initial dose of 0.5 mg. should not be exceeded.

Veratrum alkaloids are not dependent on the kidney for excretion. They may be useful in uremic coma with convulsions.

* If an excessive dose of a quaternary blocking agent is inadvertently administered, renal excretion is the only method of elimination. When the drug reduces the systolic blood pressure in severe hypertension below 120 mm. Hg, glomerular filtration may cease and no elimination of the injected or ingested dose may occur. In this situation the infusion of norepinephrine, neosynephrine, or other vasoconstrictors is necessary to restore glomerular filtration and promote excretion of the drug.

not improve the glomerular filtration rate (Vanderkolk, 1954). Consequently, it has no particular advantage in renal failure except as it may be additive in reducing the blood pressure.

The status of chlorothiazide in the treatment of hypertension with renal insufficiency is at present uncertain. It has appeared to be helpful in various forms of chronic renal disease with edema despite the fact that an acute reduction in glomerular filtration rate may follow its use. Our practice at present is to use the drug cautiously as an adjuvant to mecamylamine or other ganglion-blocking agent in cases of hypertension with renal insufficiency, but not to prescribe it as the sole antihypertensive drug unless edema is present. In any event, the nonprotein nitrogen should be watched carefully after the drug is given, and according to this index of renal function the dose of chlorothiazide is reduced or omitted.

OTHER METHODS OF TREATMENT OF RENAL INSUFFICIENCY IN HYPERTENSION

Two risks await the hypertensive patient who has impaired renal function with or without azotemia. The first risk is the continued presence of the hypertension, which in itself may accelerate vascular degeneration in the renal circulation. This can be controlled by meticulous reduction of the blood pressure as described above. The second risk is of the further destruction of renal tissue by pyelonephritis, often as a result of an ascending urinary tract infection or a hematogenous spread. The urine of patients with renal insufficiency should repeatedly be examined for evidence of infection, and if infection occurs, the patient should undergo vigorous treatment with antibiotics to preserve as much of the remaining kidney tissue as possible (see p. 45). The patient should also be instructed concerning the symptoms of urinary tract disorders and urged to come in immediately should such a complaint occur In patients with azotemia these precautions may prove lifesaving.

Treatment of azotemia can prolong life and make it more

comfortable. While nitrogen retention is not in itself the cause of the toxic uremic state, measures that reduce the nonprotein nitrogen usually make the patient more comfortable. It is possible to reduce the level of azotemia by restricting protein intake to 40 Gm. per day, by insisting on an adequate fluid intake (3,000 ml. per day), and by treating any cardiac failure that may be present. Catabolic influences tend to increase toxicity and nitrogen retention; hence infections, trauma, and corticosteroids are to be avoided. Adequate calories in the form of fats and carbohydrates should be supplied to preserve endogenous protein stores from breakdown, and external sources of protein such as gastrointestinal hemorrhage, transfusions of blood, or plasma protein infusions should be avoided if possible.

The status of the serum electrolytes should occasionally be reviewed. It will often be found that phosphate levels are elevated and the carbon dioxide combining power is reduced. Phosphate retention may be treated by the regular administration of large doses of an aluminum hydroxide preparation with meals. This reduces gastrointestinal absorption of phosphates, although it may promote constipation, particularly when ganglion-blocking agents are simultaneously being administered. If this side effect becomes troublesome, magnesium trisilicate may be combined with the aluminum hydroxide preparation. When acidosis and hyponatremia coexist, the oral administration of 1 Gm. of sodium bicarbonate three times daily may be tried for a few days. Such treatment should be given cautiously, however, since it may aggravate coexisting heart failure and edema. Some patients may experience remarkable improvement when sodium chloride or sodium bicarbonate is cautiously administered to correct hyponatremia. It may be helpful in such cases to give small infusions of hypertonic sodium chloride (250 ml. of a 2.5 per cent sodium chloride solution) while restricting fluid intake. If there is no immediate improvement, further infusions are not likely to be helpful. The same reasoning applies to the oral administration of sodium salts. If clinical improvement is to occur, it commonly appears on the first day of treatment.

Considerable controversy exists concerning the proper salt intake for a patient with renal excretory failure. Excessive loss of sodium may be a feature of some cases of terminal renal disease,

but this is less common than supposed. Occasionally the prescription of a 200 mg. sodium diet results in the "low salt syndrome" with a serious deterioration of renal function as manifested by a progressive rise in nonprotein nitrogen and by the complaints of nausea, vomiting, and weakness. More often the syndrome follows vigorous diuresis. In such patients, administration of salt may be very helpful. Unless edema is present and troublesome, it is usually wise to avoid excessive sodium loss by prescribing a sodium intake at or above the 800 mg. level daily for patients with terminal renal failure.

Serum potassium, so important to cellular and cardiac function, is fortunately regulated by a very flexible mechanism within the kidney, which provides for active tubular secretion of potassium under conditions of low glomerular filtration. In this manner, serum potassium is maintained at normal levels into the terminal phase of hypertensive renal failure. Occasionally low serum potassium results from hyperactivity of this secretory mechanism. It may also result from hypersecretion of aldosterone or large extrarenal losses of potassium. Cautious oral administration of potassium salts (potassium chloride or potassium bicarbonate 1 to 2 Gm. two to three times daily) may be useful to correct this deficiency. Intravenous administration of potassium is attended with greater risk but may sometimes be necessary. It should never be given without prior knowledge of the serum potassium level, and then it should be given very slowly, to prevent cardiac depression. In patients with oliguria or anuria, potassium should never be given either orally or intravenously and it may be important to reduce potassium-containing foods in the diet, particularly fruit juices that are high in content of this element When urine volume falls, serum potassium may rise to toxic levels within a day or two. Sharp peaked T waves appear in the electrocardiogram, and later a prolonged QRS and PR interval is noted. When the serum potassium exceeds 6 milliequivalents per liter, it is advisable to begin the administration of a sodium cycle resin by mouth or by retention enema, in a dose of 1 to 3 tablespoons 3 to 4 times daily. Serum potassium can be greatly reduced by this procedure in a matter of two or three days. In the presence of severe hyperkalemia, temporary sequestration of potassium in the liver can be accomplished by

the infusion of 20 units of insulin combined with 1,000 ml. of 5 per cent glucose solution.

When dyspnea and edema occur as a result of coexisting congestive heart failure, diuretics such as mercurial agents and chlorothiazide are not contraindicated, since the benefit to be derived from improvement in circulation and respiration far exceed any theoretical damage to the kidney that might occur from giving these diuretics to patients with azotemia. Ammonium chloride, however, should be avoided if the patient is in acidosis.

Correction of the anemia may temporarily restore well being. The use of transfusions is recommended when the hemoglobin falls below 10 Gm. If possible, red cell suspensions should be administered rather than whole blood since plasma protein is not necessary and its administration may precipitate pulmonary edema. Iron salts may be given prophylactically but usually are of little value, since iron utilization by the marrow is reduced. Cobalt may have particular usefulness in this situation as a stimulant of erythropoiesis. It is available as cobaltous chloride in association with iron salts in the commercial product Roncovite.

Use of various types of the artificial kidney in terminal renal failure has relieved many of the symptoms of uremia; in some cases it has allowed sufficient time for investigation of difficult diagnostic problems, particularly in association with unexplained oliguria or anuria. The artificial kidney has not reduced high blood pressure, but marked improvement in hypertension has followed successful renal homotransplantation (Merrill, 1956).

SUMMARY

The adverse effects of blood pressure elevation on the renal vascular bed are described and the importance of blood pressure control in the prevention of renal vascular disease is emphasized. Patients with established hypertension and renal functional impairment to less than 50 per cent of normal should be treated by the usual methods, but renal function should be carefully followed during such management to guard against progressive deterioration. If renal insufficiency is already present, reduction of the blood pressure must be accomplished more slowly, but usually it is possible to achieve an equivalent degree of blood pres-

sure reduction with ganglion-blocking agents and other adjuvants of treatment without a permanent exacerbation of the renal insufficiency. In addition to reduction of the blood pressure in patients with hypertension and azotemia, much can be accomplished by careful adjustment of electrolyte abnormalities and treatment of cardiac failure, anemia, and other factors that contribute to the disability caused by terminal uremia.



CHAPTER 16



Malignant Hypertension: Diagnosis, Prognosis, and Treatment

A malignant complication of hypertensive disease is a well-recognized entity. This so-called accelerated phase of hypertension is defined as occurring whenever a sustained, severe elevation in diastolic blood pressure is associated with papilledema. Cardiac, cerebral, and renal lesions may also occur but are not usually considered diagnostic since they are often preceded by the retinal lesions that establish the diagnosis. If possible one should anticipate this complication by identifying it in the "premalignant" phase, which is usually identified by the onset of visual difficulty, and the appearance of fresh hemorrhages and exudates in the retina in association with a severe elevation of pressure. Renal function deteriorates rapidly at about the time of onset of this complication. Chronic glomerulonephritis and pyelonephritis acquire the pattern of malignant hypertension when renal failure in these conditions becomes advanced. In the later stages differentiation of these diseases from the malignant phase of essential hypertension can be made only with difficulty, as described previously (p. 42). In the experimental animal the accelerated form of hypertensive disease is noticed whenever severe hypertension is associated with evidences of renal failure (Goldblatt, 1940). It is possible that malignant hypertension is

TABLE 10. MALIGNANT HYPERTENSION: SURVIVAL WITH AND WITHOUT DRUG TREATMENT

Reference	*Total cases, number*	*Time observed*	*Survival*		*Remarks*
			Months	*Percentage*	
		CONTROL SERIES			
Keith, Wagener, Kernohan (1928)	81	*	15	14	10 cases with blood urea always over 40
Schottstaedt and Sokolow (1953)	104	**	18	11	Includes all cases regardless of renal function
McMichael (1955)	30	?	15	15	Other details unspecified. Blood urea below 100 mg. per cent
		DRUG TREATMENT			
McMichael (1955)	32	***	15	42	Same selection as above. Methonium treated
Smirk (1958)	43	***	15	75	Details not specified. Methonium treated
Schroeder, Morrow, Perry (1954)	68	***	15	80	59 per cent if also included are 28 additional patients who stopped treatment, of whom 25 died
	41	***	15	83	Cases with initial azotemia are excluded

* From the first hospital admission until death.
** From diagnosis until death.
*** From the beginning of treatment until death.

a consequence of prolonged high blood pressure within the renal arteries. Pickering (1952) has adopted this view, although others do not accept his opinion unequivocally since many hypertensive individuals may sustain very high blood pressure levels for many years without developing the syndrome. Perera (1956) believes that the accelerated form of hypertension is a manifestation of arteriolar disease, as distinct from the large artery involvement of the more benign phase of hypertension. Certainly a generalized necrotizing arteriolar lesion is a typical finding at autopsy. This feature is most prominent in the renal vascular bed and accounts for the frequency of renal failure, which often appears very shortly after the onset of malignant hypertension. From the evidence available it must be concluded that both severe hypertension and a significant disturbance of renal circulation are common prerequisites to the development of human malignant hypertension; consequently, either reduction of the blood pressure or prevention of renal insufficiency should lead to the elimination of this complication.

In the original description by Keith, Wagener, and Kernohan (1928) 86 per cent of subjects with malignant hypertension died within 15 months Twelve per cent already had azotemia at the beginning of the interval of observation. When such cases are included the survival rate for the untreated disease varies from 11 to 15 per cent (Table 10). In these studies it was generally agreed that spontaneous remissions were exceptional.

EFFECTIVENESS OF BLOOD PRESSURE REDUCTION IN THE TREATMENT OF MALIGNANT HYPERTENSION

In a series of cases treated by surgical intervention the patients in whom the diastolic blood pressure was reduced more than 20 mm. Hg had a slightly better rate of survival than did those in whom the blood pressure was not reduced by the operation (Hoobler, 1951). The 15-month survival rate of 70 per cent that Smithwick (1956) reported to follow after sympathectomy in group 4 hypertension shows that blood pressure reduction has some effect on the prognosis. Other efforts to reduce the mortality rate in this disease have been reported by Newborg and Kempner (1955) using the rice diet, and by Page, Taylor, and Corcoran

(1951) using pyrogen treatment to lower the blood pressure. It is probable that all these therapeutic measures acted by reducing intravascular pressure for sufficient periods of time to cause a remission in the process of vascular deterioration, which is usually rapid in the accelerated phase of hypertensive disease.

Since more effective methods have become available the effect of blood pressure reduction on the prognosis in malignant hypertension has been the basis of several reports. Table 10 summarizes some of the findings and shows clearly that blood pressure *reduction prolongs survival in this most serious complication* of hypertension.

Control of the Blood Pressure

It is clear that in no other hypertensive condition does survival depend so much on effective treatment Considerations of convenience, expense, or disabling side effects are less important than the preservation of life itself. Since the disease is rapidly progressive, no time should be wasted in attempting to achieve reduction of blood pressure by uncertain techniques when the means is at hand for immediate and effective blood pressure reduction by using ganglion-blocking drugs and their adjuvants. The mainstay of treatment is a ganglion-blocking agent combined with chlorothiazide in such a manner as to reduce the standing blood pressure to normal levels as promptly as renal function will permit (see Appendix 7, p. 278).

Once this has been maintained for a period of several weeks it is possible, although not recommended, to experiment cautiously with other forms of treatment. If this is attempted very careful supervision of the blood pressure must be maintained, since even a few days of hypertensive "rebound" may lead to a fatal termination. If the ultimate long-term control by ganglion-blocking drugs is difficult or unsatisfactory, or if the patient does not co-operate in the medical regimen, sympathectomy may *offer certain advantages*

When one commences treatment in a patient who demonstrates some degree of azotemia, with a nonprotein nitrogen level ranging between 50 and 100 mg per cent, the goal of achieving normotension must be approached more carefully, but nothing short of a clearly progressive azotemia should be allowed

to modify the efforts to achieve a normal blood pressure. Frequently it is useful to initiate treatment with parenteral chlorisondamine or pentolinium (Appendix 5, p. 273), particularly if severe pressure-dependent symptoms are present. When normal blood pressures have been achieved by this method it is possible to convert the patient to orally administered ganglion-blocking agents of which mecamylamine is preferred. If this drug causes such side effects as tremor or mental confusion, chlorisondamine or trimethidinium may be substituted but under no circumstances should the blood pressure be allowed to rise to pretreatment levels. The additional use of chlorothiazide, 0.5 Gm. two to three times daily, so reduces the requirement of ganglion-blocking agents that control of the blood pressure is usually possible without unacceptable side effects to the patient.

The effectiveness of treatment can be gauged by numerous evidences of clinical improvement. Almost immediately pressure-dependent symptoms such as dyspnea, mental confusion, and headaches are relieved. After several weeks, visual improvement is noticed and albuminuria and hematuria decrease. After a month or more the x-ray examination of the chest will reveal a diminution in heart size. Renal function, which may temporarily have become worse, will return either to pretreatment levels or above. The patient acquires better understanding of the regimen, and his records of blood pressures taken twice daily in the home will show smoother regulation than at the beginning of the treatment. If no serious renal complication has set in, he is relatively free of the immediate risk of death. The only unpredictable danger lies in the usually continued elevation of the recumbent blood pressure, which carries the risk of cerebral hemorrhage in the night. For this reason a treatment program that would guarantee recumbent normotension would be most advantageous.

The additive use of hydralazine with a ganglion-blocking agent has been reported by Perry and Schroeder (1956) to achieve this aim. The original regimen required a combination of oral hexamethonium in doses up to 1 to 2 Gm. every 4 hours with hydralazine given at the rate of 100 mg. every 4 hours. According to their studies, such a program resulted in reducing the sitting as well as the standing blood pressure to normal levels, and over a period of time led to a considerable reduction in the

requirement of hexamethonium and even of hydralazine. As a result, at the end of 2 to 3 years 19 patients had been able to omit hexamethonium entirely and to reduce substantially the daily doses of hydralazine without a resurgence of the blood pressure. Although this group represents only a small percentage of those who started on such treatment, this finding is indeed impressive and deserves careful evaluation. Unfortunately no records of recumbent blood pressure were recorded but it is likely that these too were normal in the majority of the patients achieving these satisfactory results.

Statistics of Rast and Orgain (1955) support further the view that the addition of hydralazine improves blood pressure control and reduces the requirement of ganglion-blocking agents. While there was considerable reduction in recumbent blood pressures, evidence of completely normal supine readings was not reported in this study.

At the University of Michigan Hypertension Clinic it has not been possible during a treatment period of 6 months or longer to demonstrate that the orthostatic gradient of blood pressure was greatly diminished when hydralazine was added to the regimen of a patient previously treated with mecamylamine, although the requirement for the latter drug was substantially reduced. While this experience would tend to deny the added value of hydralazine in creating recumbent normotension in a case of severe established or malignant hypertension, a number of possibly significant alterations from the original regimen were practiced in our study. Neither drug was given in as large or as frequent doses as recommended by Perry and Schroeder; the blood pressure was not forced to such low levels during initial phases of treatment; the treatment was not maintained for such long periods of time; and mecamylamine or chlorisondamine was substituted for hexamethonium, the drug that was used in the original study, and that now seems to have been superseded by more effective ganglion-blocking agents. While any one of these elements might have been a factor in reducing the effectiveness of the treatment program, and in explaining our failure to confirm the value of adding hydralazine to ganglion blockade in the treatment of malignant hypertension, there is much to be said for a treatment program that gives such impressive results

as those described by Schroeder and Perry. For this reason a modification of the original treatment schedule, which takes advantage of the longer-acting ganglion-blocking drugs, is included in Appendix 11 (p. 299). Certainly this treatment would be recommended in the event that the use of ganglion blockade or sympathectomy in addition to chlorothiazide was not effective in maintaining orthostatic normotension and some reduction in recumbent blood pressures continuously throughout the period of treatment of the patient with malignant hypertension.

To illustrate the effectiveness of ganglionic blocking agents and chlorothiazide in the management of malignant hypertension the following case history is presented:

Case History

A 30-year-old man was admitted to the University Hospital in October, 1955, with fatigue, dyspnea, and ankle edema of one year's duration. He had lost 35 pounds in the preceding 8 months and had noted progressive blurring of vision during this period. On admission, his blood pressure was 220/168 mm. Hg. Funduscopic examination revealed 2 diopters of papilledema with many fresh hemorrhages and exudates. The retinal arterioles were the site of severe vasoconstriction. The heart was greatly enlarged and exhibited a gallop rhythm Lungs were clear but the liver was palpable and there was some pretibial edema. Examination of the urine revealed a 3-plus albuminuria. The nonprotein nitrogen was 54 mg. per cent. The serum creatinine was 2.59 mg. per cent with a clearance of 35 liters per 24 hours (normal 130–140 liters). The hemoglobin was 10.5 Gm. Intravenous pyelograms showed faint visualization but were otherwise normal.

The patient was instructed in the technique of blood pressure recording in the home, and discharged on a total daily dose of 10 mg. of mecamylamine. During the following two years he kept careful records, which during the first year showed standing blood pressure readings in the range of 110/90 mm. Hg to 150/120 mm. with recumbent readings always above 200/120 mm. Hg. To achieve this degree of control it had been necessary to increase the dose of mecamylamine to 20 mg. or more three times daily. Addition or withdrawal of reserpine did not alter the

blood pressure or the mecamylamine requirement. With appropriate daily laxatives normal bowel function was maintained.

Dryness of the mouth was a most distressing complaint. The nonprotein nitrogen, which had risen to 73 mg. per cent two months after starting the treatment, fell to 63 mg per cent 10 months later. The symptoms related to hypertension, except for the fatigue, cleared completely. Papilledema disappeared and fresh exudates and hemorrhages were no longer seen in the ocular fundi although the retinal arterial changes persisted. The heart became smaller. Urinalysis revealed only a slight trace of albumin.

Because of the persisting recumbent hypertension and the generally serious prognosis, hydralazine was added to the regimen at this time. The mecamylamine requirement gradually fell from 70 to 40 mg daily as the hydralazine dose was increased to 150 mg. 4 times daily. The blood pressure was maintained at 180/128 mm. Hg recumbent, and 120/84 mm. standing. A mild degree of edema appeared. The last nonprotein nitrogen was 74 mg. per cent. To test the effectiveness of hydralazine this drug was gradually withdrawn. Recumbent blood pressure was unchanged but the ankle edema cleared. The hydralazine was nevertheless restored. When chlorothiazide became available a dose of 0.5 Gm. twice daily reduced the mecamylamine requirement by one half. Because of continued dry mouth, blurred vision, and constipation, trimethidinium methosulphate was recently substituted for the mecamylamine in a dose of 40 mg. twice daily. The standing blood pressure rose slightly to 140–154/90–102 mm. Hg but fell again to 110/78 mm. when 20 mg. of mecamylamine twice daily was substituted. During further trial of the new blocking agent trimethidinium in larger dosage the constipation and dry mouth disappeared completely and the blood pressure was well controlled but the recumbent blood pressure was still elevated to 180–190/118–122 mm. Hg.

COMMENT. It would be agreed by all observers that without treatment the life expectancy of this patient with malignant hypertension and azotemia was short indeed. Despite many side effects vigorous treatment, supervised by blood pressure readings carefully performed by the patient at home, has resulted in a

remission of the signs of malignant hypertension with almost complete cessation of the albuminuria and retinopathy. Renal function has shown no improvement and the prognosis is still serious. Hydralazine was of little added value; mecamylamine was the mainstay of treatment until trimethidinium became available and reduced the severity of the side effects. The addition of chlorothiazide reduced the necessary dose of other antihypertensive drugs.

SUMMARY

Malignant hypertension is recognized as the most serious complication of hypertensive disease. The mortality rate in this condition is between 85 and 90 per cent within 15 months if no treatment is given, while it falls to 20 per cent when effective blood pressure reduction is maintained by the use of ganglion-blocking agents. In no other complication is the prompt and continued use of effective antihypertensive therapy as important as in this condition. The use of chlorothiazide and ganglion-blocking agents with or without the additional use of hydralazine and sympathectomy is recommended.



CHAPTER 17



Toxemia of Pregnancy

Toxemia, as a complication of hypertensive disease, is said to appear when in the latter half of pregnancy there is a distinct rise in blood pressure together with the appearance of albuminuria and an unusual gain in weight. When all three manifestations occur the diagnosis may be made with certainty, when two of these findings appear the diagnosis of toxemia is probably correct, and it should certainly be seriously considered when any one of the three signs appears. In point of time, edema or an abnormal gain in weight is probably the first evidence of this complication but it is easier to recognize the other deviations from the normal course of pregnancy. Emphasis should be placed on the development of these abnormal findings during the latter half of pregnancy. For example, the occurrence of hypertension or albuminuria during the first trimester does not permit the diagnosis of toxemia since such findings at this stage indicate previous disease. An increase in pre-existing albuminuria or hypertension during the latter half of pregnancy, however, means that a true toxemia has been superimposed upon the previously abnormal state.

PATHOGENESIS

Although little is known about the cause of toxemia, a current belief is that it follows the release of some unknown toxic sub-

stance from an ischemic placenta, and that this substance raises the blood pressure, alters capillary permeability, and thereby produces albuminuria and salt retention. This theory is supported by the fact that the placenta is necessary for toxemia to occur, that it occurs more frequently in diseases which lead to vascular insufficiency such as hypertension and diabetes, and that infarction of the placenta is seen more commonly in toxemic than in normal pregnancies. Some students of this subject believe that pregnancy brings out prematurely a hypertensive disease process that otherwise would have overtaken the genetically predisposed woman in later years. Certainly it is true that in populations in which familial hypertension is common, toxemia of pregnancy is unusually frequent. Furthermore, the type of hypertension that has its origin in toxemia appears in later years to differ in no important characteristic from essential hypertension arising *de novo*.

THE RISK OF TOXEMIA IN THE HYPERTENSIVE WOMAN

In the studies of Dexter and Weiss (1941), the risk of toxemia in the pregnant hypertensive woman appeared to be about 50 per cent and in half of these cases the hypertensive disease ultimately become more severe as a result of the toxemia. They noted that when the pregnancy was interrupted within three weeks from the onset of uncontrolled toxemia, the risk of a permanent exacerbation of the hypertension was substantially reduced. The fetal mortality was as high as 50 per cent, but this also depended upon the severity of the toxemia and its duration. Undoubtedly the risk to both mother and child is proportional to the severity of the hypertension before pregnancy. In patients with mild elevations of blood pressure the risk of toxemia or of a permanent exacerbation of hypertensive disease is minimal. Furthermore, with the improvement in treatment that has occurred since the studies of Dexter and Weiss, a considerably better prognosis can now be given and very few patients should be denied a trial of pregnancy because of pre-existing mild or moderately severe hypertensive disease without vascular complications.

RECOMMENDATIONS CONCERNING PREGNANCY IN CASES OF HYPERTENSION

At the University of Michigan Hospital it has been the practice not to advise against pregnancy unless the hypertension is of the severe established variety or unless serious vascular complications have occurred. In previous years patients with blood pressure in the severe and moderately severe established categories, who desired to have a pregnancy, were advised to undergo sympathectomy. If the blood pressure fell to near normal levels it was the subsequent experience that pregnancy could be completed without difficulty (Peet, 1948). This experience would suggest that the toxemic complication of hypertension is to some extent dependent upon the blood pressure level itself. If this is the case, it should be possible with current methods of management to carry most hypertensive women through pregnancy since their blood pressure can usually be maintained at nearly normal levels during pregnancy. This assumption is based chiefly on the results that followed successful sympathectomy and does not necessarily apply to cases where the blood pressure is normalized by drug treatment.

In the hypertensive patient who has become pregnant, frequent determination of the blood pressure is mandatory, together with regular recording of the weight and of urinalyses performed repeatedly throughout the pregnancy. When such observations are commenced in the early months of pregnancy it is possible to recognize early deviations from the normal more accurately and to institute appropriate treatment in time. The blood pressure of the hypertensive patient should be kept as near normal as possible throughout her pregnancy by the intensive use of sodium restriction, the continuous administration of chlorothiazide, and the additional use of rauwolfia alkaloids and hydralazine if necessary. Should signs of toxemia nevertheless develop it is necessary for the patient to be hospitalized for further sodium restriction, increased doses of rauwolfia alkaloids, and the added effect of strict bed rest. If the expected improvement does not occur one should prescribe veratrum alkaloids (Appendix 5, p. 268; Appendix 8, p. 289) and as a last resort ganglion-blocking

agents (Appendix 5, p. 270). If the recumbent blood pressure cannot be kept below the level of 150/100 mm. Hg, or if albuminuria and weight gain continue, interruption of pregnancy should be considered, particularly if the fetus is old enough to survive. It should be recalled that a period of more than two to three weeks of uncontrolled high blood pressure during toxemia of pregnancy not only may produce a permanent exacerbation of hypertension in the mother, but also is very likely to cause the death of the infant.

Antihypertensive treatment may have to be continued after the delivery to avoid occasional acute postpartum increases in blood pressure. Usually, however, there is a gradual reduction in the pressure so that after two to three months the patient will have regained a normal level. If hypertension persists after the third or fourth month of postpartum observation it is not likely that blood pressure reduction will ensue at a later date. The patient should then be treated in the same way as the usual hypertensive subject It is encouraging to know that such residual hypertension usually remains relatively benign and frequently responds to sympathectomy or drug treatment.

TREATMENT OF THE HYPERTENSION ACCOMPANYING TOXEMIA OF PREGNANCY

Since toxemia is at least partially a blood-pressure-dependent condition, and since many of the manifestations of the disease can be controlled by reducing the blood pressure, antihypertensive treatment should be pursued vigorously in the presence of this complication. For the acute management of severe toxemia it is useful to prescribe parenteral reserpine (Appendix 6, p. 277) together with chlorothiazide 0.5 Gm. two to three times daily for the remainder of the pregnancy. The hypotensive effects of chlorothiazide may be delayed; consequently this drug should not be withdrawn if it does not seem immediately effective. The effects of parenteral reserpine on the other hand should be apparent within one-half to one hour and should give rise to a substantial reduction of the blood pressure as well as a considerable sedative effect. If, despite the administration of this agent every 4 to 6 hours in doses of 2.5 to 5 mg. intramuscularly, a reduction

of blood pressure below 160/110 mm. Hg is not observed, the risk of an eclamptic convulsion is still present and treatment with veratrum alkaloids either intravenously or parenterally should be attempted (p. 268). It is also possible to give veratrum by the oral route (Appendix 8, p. 289) and this treatment, together with sedatives, rauwolfia, chlorothiazide, and bed rest usually suffice to bring the blood pressure within levels not likely to result in eclampsia. If an effective blood pressure reduction does not occur after such treatment for several days, ganglion-blocking agents may be given. However, the report of Morris (1953) suggests that quatenary ganglion-blocking agents may increase fetal mortality, since they may lead to drying of secretions and an increased incidence of pneumonia in the fetus. Mecamylamine, which has a greater tendency to intracellular penetration, may also have an adverse effect in pregnancy. For these reasons it is preferable to withhold these drugs until other antihypertensive agents have been tried.

SUMMARY

Toxemia of pregnancy is more likely to occur in hypertensive women but with current treatment methods pregnancy may be permitted except in cases of severe hypertensive disease. Prophylactic treatment with salt restriction, chlorothiazide, and reserpine is indicated. If toxemia nevertheless occurs, the additional prescription of strict bed rest, parenteral reserpine, or veratrum is indicated and the pregnancy should be interrupted if possible after more than three weeks of unsuccessful treatment. The hypertensive disease that follows toxemia of pregnancy is relatively benign and often responds to sympathectomy.

CHAPTER 18

Reduction of the Blood Pressure in Hypertensive Emergencies

EMERGENCIES REQUIRING IMMEDIATE TREATMENT

The situations in which urgent treatment of hypertension are necessary may be classified as acute crises, in which failure to act within 30 to 40 minutes may compromise the life of the patient, and as conditions in which reduction of the blood pressure in a matter of hours is sufficient to protect the patient from a grave complication of the disease. Among the serious crises that require immediate efforts to lower the blood pressure are the following: (1) mental confusion and convulsive movements heralding the onset of a convulsive seizure, (2) a focal or generalized neurologic sign or symptom of an impending acute cerebrovascular episode, (3) the abrupt occurrence of a severe generalized occipital headache with stiff neck and other warning of impending cerebral hemorrhage, (4) the onset of acute pulmonary edema. Treatment is slightly less urgent when severe hypertension is associated with the following circumstances: (1) a moderate degree of dyspnea and orthopnea, (2) severe epistaxis, and (3) failure of the blood pressure to fall from excessive levels after several hours of bed rest.

TECHNIQUES OF TREATMENT

In Table 11 and in Appendix 5, p. 266, a summary of alternative treatment methods and of details concerning the use of each drug is presented. For the greatest emergencies the use of Arfonad by intravenous drip, parenteral sodium nitroprusside, intravenous hexamethonium, protoveratrine, and parenteral reserpine all have particular advantages that require some discussion.

TABLE 11. CHOICE OF TECHNIQUES TO LOWER BLOOD PRESSURE IN HYPERTENSIVE EMERGENCIES

	Relative action			
Drug and technique	*Rapidity*	*Magnitude*	*Duration*	*Side effects*
Arfonad I. V. 4–20 mg /min.	+++	+++	+	+
Sodium Nitroprusside I. V 50 μg /min.	+++	+	+	+
Hexamethonium I. V 1.0 mg /min	++	+++	++	+++
Protoveratrine A. and B I V. 1.0 μg./min.	++	+++	++	+++
Reserpine 5 0 mg. I. V. or S. C	+	+	+++	+++
Hexamethonium S. C. 2 5 mg.; double dose every half hour	+	+++	+++	+++

I. V. = Intravenously I M = Intramuscularly. S C = Subcutaneously.

The simplest procedure, and one that is applicable when the patient is seen outside the hospital, is to give parenteral *reserpine* in a dose of 2 5 to 5 mg. intramuscularly. This treatment will usually produce a blood pressure reduction of 20 to 50 mm. Hg within the first one or two hours, but severe hypotension does not occur and minute-to-minute supervision of the blood pressure is not necessary. The drug also produces the side effects of sedation and somnolence that are usually advantageous. In certain situations, particularly when one is watching for changes in neurological findings, this effect may be a disadvantage. Furthermore, there is a 30- to 45-minute delay in hypotensive action and the blood pressure reduction is often insufficient to achieve the purpose of the initial treatment.

Because of this uncertainty of action it is preferable to use more effective treatment for the serious hypertensive emergency,

particularly when the patient is in the hospital. To obtain an immediate and considerable reduction in blood pressure, which is nevertheless quite controllable, *Arfonad* may be given by intravenous drip so arranged that from 4 to 20 mg. of the drug can be infused per minute (Appendix 5, p. 266). This technique usually relieves in a matter of a few minutes many blood-pressure-dependent symptoms of both cardiac and cerebral origin (Sarnoff, 1952). It is also useful when it is desired to maintain deliberately a subnormal blood pressure, as in the treatment of nasal or subarachnoid hemorrhage. The use of this drug has the further advantage that if the hypotension proves deleterious to the patient the effects on the blood pressure disappear within 10 to 20 minutes after stopping the infusion. Because of this marked response of the blood pressure to both increases and decreases in the rate of infusion, it is necessary to supervise the blood pressure almost continuously while the drug is being administered. It is probably inadvisable to prolong the use of Arfonad beyond 36 to 48 hours, but otherwise there are no particular contraindications to its use in hypertensive emergencies. Since Arfonad acts by ganglion-blocking effects, as well as by a moderate vasodilator action, it may not be effective in patients who have become tolerant to ganglion-blocking agents, and prolonged use will cause the usual parasympathetic side effects such as dry mouth, bladder weakness, and ileus. These actions are usually not prominent during short-term administration but must be considered when control of the blood pressure is to be maintained for several days.

If a refractory state has developed to Arfonad or other ganglion-blocking agents, the patient may respond to *sodium nitroprusside* given intravenously (Appendix 5, p. 267). Continuous supervision of the drip rate is also necessary to establish certain control of the blood pressure and to avoid extreme hypotension with this drug (p. 267). Since nitroprusside acts directly on vascular smooth muscle it is effective in patients refractory to ganglionic blockade and it has the further advantage of avoiding the parasympathetic side effects associated with Arfonad. In our limited experience, however, nitroprusside has proved to be a relatively weak vasodepressor.

When rapid reduction of the blood pressure is unquestionably

desirable, but it is not feasible to supervise the administration of the drug for a long *period* of time, the *program outlined by* Freis (1952) for the intravenous administration of *hexamethonium* may be employed (Appendix 5, p. 270). This requires the minute-by-minute administration of hexamethonium intravenously until the proper reduction in blood pressure is achieved preferably *in the sitting position. A satisfactory objective*, which should relieve most blood-pressure-dependent emergencies and yet avoid the risk of severe hypotension, is to lower the blood pressure one half of the way from its starting value to upper normal levels. When this degree of reduction has been secured, the total cumulative *intravenous dose may then be prescribed* subcutaneously every 4 to 6 hours as necessary to keep the blood pressure below a predetermined level. By this means it is possible to maintain blood pressure reduction for at least the first several days of treatment.

For the *lesser emergencies mentioned* above, in which 3 to 4 hours may safely elapse before a blood pressure reduction is achieved, *reserpine* or ganglion-blocking agents may be administered by the intramuscular or subcutaneous route. If a dose of 2 5 to 5 mg of reserpine is not effective in achieving a substantial blood pressure reduction within an hour or so, *hexamethonium* may be given in gradually increasing subcutaneous doses as out*lined in* Appendix 5, p. 272. When the *desired* blood pressure reduction is obtained the last dose administered may be repeated every 4 to 6 hours as necessary if any increase in the blood pressure above a desired level occurs. Once a satisfactory result has been secured, a longer-acting ganglion-blocking agent may be substituted for hexamethonium. *Either pentolinium or chlorisondamine* may be substituted in doses one fifth of those required for hexamethonium. It is usually found that injections of the longer-acting agents at 8- to 12-hour intervals will suffice to control the blood pressure. The frequency and magnitude of dosage of these ganglion-blocking agents depends on renal excretory efficiency. Furthermore, patients with increased cerebrospinal fluid pressure appear to be *unusually sensitive to ganglion* blockade and may respond with excessive hypotension to conventional doses. Since the renal or cerebral status of the hypertensive patient requiring emergency treatment may not be known

when it is necessary to give these drugs by injection, the program of a graded increase in dosage has been outlined with the full knowledge that the first one or two doses will often prove ineffective in patients not unusually sensitive to ganglion blockade. If the patient is hypersensitive to these agents, a marked blood pressure reduction will usually follow the first intravenous or parenteral injection. Therefore, such patients should never be *left unattended during the 15 to 30 minutes that follow the first* injection of a potent ganglion-blocking drug, for syncope may *develop without warning and if the patient is left unattended* even briefly he may lapse into irreversible vascular collapse. On the other hand, if the acute hypotensive episode is immediately recognized, restoration of the blood pressure can be accomplished immediately by placing the patient in a head-down tilt and administering relatively small doses of vasopressor drugs such as norepinephrine or neosynephrine (see footnote, Appendix 7, p. 288).

The pure alkaloids *protoveratrine* A and B are effective in lowering the blood pressure even in patients refractory to ganglion-blocking agents. Unfortunately, because of the delay between the time of injection and the appearance of the first effect, it is often difficult to arrive at the critical dose that must first be given if the blood pressure is to respond. The program outlined in Appendix 5, p. 268, is adapted from Meilman's reports (1952) and our own experience (Hoobler, 1950). When a proper dose has been given reduction in blood pressure will occur within 6 to 8 minutes and be sustained for 30 to 40 minutes. This reduction in blood pressure is probably accomplished through carotid sinus afferent nerve stimulation as well as by increasing the discharge from the coronary chemoreceptors and other afferent impulses to the nodose ganglion. Alterations in central vasomotor regulation result in reductions in cardiac output and sometimes in total peripheral resistance, together with a consistent sinus bradycardia that may progress to varying degrees of heart block in the presence of overdosage (Hoobler, 1952, 1955). Unfortunately, emetic centers are also stimulated and prolonged blood pressure reduction by either intravenous or oral administration of these agents is usually associated with a high frequency of nausea and vomiting, even though single intrave-

nous injections are rarely associated with such side effects. The bradycardia and cardiac rhythm disturbances are abolished instantly by the intravenous administration of 1 mg. of atropine sulfate. Emesis may be relieved somewhat by this procedure and some alleviation of extreme hypotension also follows administration of atropine.

Veratrum is a time-tested remedy for toxemia of pregnancy (Meilman, 1953) and a hypotensive response will occur in every patient provided an adequate dose is given. For short periods of reduction in blood pressure, this agent is effective and safe; for longer periods of control, other drugs are preferable. When rapid heart action is associated with hypertensive crises the bradycrotic and inotropic effects of the veratrum alkaloid may be particularly useful.

SUMMARY

In acute emergencies control of the blood pressure is best accomplished by the intravenous infusion of Arfonad, nitroprusside, or graded doses of hexamethonium provided the means for close blood pressure supervision are at hand. Extreme hypotension and the necessity for close supervision of the blood pressure can be avoided by using parenteral reserpine, but this drug is less dependable when blood pressure reduction is urgent. Intravenous veratrum has a special sphere of usefulness in acute emergencies, especially with toxemia of pregnancy. A detailed program for more gradual reduction of the blood pressure in less urgent situations by parenteral ganglion-blocking agents is also described.

SECTION V

USE OF SPECIFIC TREATMENT REGIMENS TO REDUCE THE BLOOD PRESSURE



CHAPTER 19



Chlorothiazide

PHARMACODYNAMICS

Chlorothiazide is an orally active diuretic that appears to inhibit the renal reabsorption of water, sodium, chloride, and to a lesser extent potassium, by mechanisms similar to those involved in the diuretic action of acetazolamide and mercury (Ford, 1957). In the nonedematous subject a fluid loss of 2 to 4 pounds can be expected when 1.0 Gm. is administered twice daily for one to three days. The effects of single doses do not last more than 6 hours, and the drug must be administered daily without interruption for optimum effect. The effect is maintained indefinitely by 0 5 Gm. two or three times daily although a large intake of sodium chloride tends to nullify the effects of the drug in maintaining salt depletion. In short term experiments a 10 to 20 per cent reduction in plasma volume and extracellular fluid is observed (Tapia, 1957), and concomitant reductions in renal plasma flow and glomerular filtration rate occur (Crosley, 1957). Serum sodium levels are usually maintained but carbon dioxide combining power increases, (Weller, 1958) and serum potassium levels may fall when large doses of the drug are administered. This reduction in potassium may be prevented by giving potassium chloride or fruit juice supplements, or by prescribing the medication in the morning and at bedtime so that the potassium intake of the evening meal is retained. After a certain reduction in body fluid volume has been achieved, further depletion is

prevented by other mechanisms as yet unknown. Ingestion of moderate amounts of sodium chloride in the diet (1 to 2 Gm. daily) usually does not overcome the effects of salt depletion although a greater intake of these electrolytes will result in salt repletion (Freis, 1957; Wilkins, 1957) and cancellation of the depressor effect of chlorothiazide on the circulation. Remarkably few toxic effects have been observed. Leukopenia or anemia, which occurs occasionally after the use of other sulfonamide derivatives, has not been reported to date, but nausea, vomiting, and skin eruptions have rarely occurred. An occasional patient complains of dizziness and weakness, presumably from hypotension and sodium or potassium depletion.

EFFECT OF CHLOROTHIAZIDE IN HYPERTENSION

The effect of chlorothiazide in the control of hypertension may be considered in three situations. As a sole antihypertensive agent, it is effective in reducing the blood pressure in about one fourth to one half of cases with milder forms of hypertension (Freis, 1957). This occurs especially when the disease is associated with occult or manifest edema, as in hypertension following steroid administration. The frequency of blood pressure reduction, when chlorothiazide is used in this manner, approximately corresponds to the results to be expected in a group of patients with essential hypertension subjected to a 200 mg. sodium diet. Because of the ease of administration and its effect in mild hypertension, this drug may be useful in the early stages of the disease.

A second and rather regular effect is observed when chlorothiazide is used in conjunction with ganglion-blocking agents. The author's experience conforms to that of Moyer (1958), who states that the drug reduces the requirement for ganglion-blocking agents by 50 per cent in the majority of patients who are under such treatment. It also potentiates the effects of previous sympathectomy, so that patients who have responded partially or not at all to surgical treatment exhibit significantly reduced standing blood pressure levels (Weller, 1959). In view of this fact, patients are now started on ganglion-blocking agents only after three days of salt and water depletion with chlorothiazide;

if the patient is already taking such drugs, chlorothiazide is added to the regimen with a careful admonition to reduce the dosage of the ganglion-blocking agent promptly, as soon as the blood pressure begins to fall. The response may appear within a few hours or days. The sensitization effect is retained when maintenance doses are prescribed, but cessation of chlorothiazide treatment may result in an abrupt and possibly disastrous rebound of the blood pressure. The medication should be discontinued only under careful supervision. The sensitizing effects of chlorothiazide are similar to those noted when mercurial diuretics are given to a hypertensive patient simultaneously receiving a ganglion-blocking agent. The fall in blood pressure is frequently greater in the standing than in the recumbent position.

Finally, this drug is reported to potentiate other antihypertensive agents. Thus the effects of hydralazine, reserpine, and veratrum are said to be magnified by chlorothiazide. These claims are hard to evaluate, particularly if one attempts to distinguish between an additive and a potentiating effect. Because of the freedom from side effects there appears to be no reason why combination regimens should not be used, provided it is demonstrated by trial that each drug is necessary to achieve the desired blood pressure reduction.

The author prefers to try chlorothiazide with or without reserpine in cases of mild to severe established hypertension and in arteriosclerotic hypertension, and to use chlorothiazide without reserpine after sympathectomy or whenever there is an indication for the use of ganglion-blocking agents, since the reduced requirement for these drugs alleviates many of the distressing side effects of parasympathetic blockade. If the drug is to be effective, careful blood pressure observations will establish this fact within a few weeks; prolonged therapeutic trial or precise dosage adjustment does not seem necessary In an occasional refractory case an increase in daily dosage to 2 to 3 Gm for a few weeks may provide the desired response, but in the light of our present knowledge it is not believed necessary to give doses in excess of 1.0 Gm. daily for prolonged periods.

Despite its profound pharmacologic actions, chlorothiazide has not yet produced serious effects. Potassium depletion and an increase in azotemia are seen occasionally in susceptible persons.

Therefore, an effort should be made to preserve or augment potassium intake, particularly when large maintenance doses are prescribed. In patients with azotemia, renal function should be followed carefully, but since chronic nephritis with edema responds to treatment, renal excretory failure cannot be considered an absolute contraindication to its use. In hypertensive patients with a history of cardiac disability, the drug would appear to possess particularly beneficial effects. If digitalis is being taken, potassium depletion should be carefully avoided since such deficiency may lead to rhythm disturbances. The effect of the drug on the cerebral complications of hypertension is difficult to evaluate at present, but serious postural hypotension or syncope should obviously be avoided in those patients liable to cerebrovascular thrombosis. The drug is obviously useful in malignant hypertension, not as the sole treatment, but in an effort to reduce the requirement for ganglion-blocking agents.

The unknown but ever-present danger of cumulative toxic effects cannot as yet be estimated. After more than a year of usage, chlorothiazide still appears to be remarkably safe and effective in the treatment of hypertension.

SUMMARY

Chlorothiazide is an effective oral diuretic and saluretic drug with negligible side effects. As the sole antihypertensive agent it is effective in reducing blood pressure in many cases of mild and moderately severe hypertension and in the arteriosclerotic form of the disease. It potentiates the actions of ganglion-blocking agents so effectively that the dose of these drugs may be greatly reduced and their side actions minimized. It may also prove useful in combination with other antihypertensive drugs.

CHAPTER 20

Rauwolfia Alkaloids

PHARMACODYNAMICS

The rauwolfia alkaloids have a unique mode of action. It would appear that they act centrally by stimulating those hypothalamic centers which control autonomic activity. Vagomimetic action is manifested by the decreased pulse rate and increased gastrointestinal activity; sympathetic inhibition is revealed by vasodilation in the nares and by reduction in the blood pressure. Accessory effects on the hypothalamic area include the so-called tranquilizing action, and an increased appetite, with a tendency to gain weight that is unrelated to any suppression of thyroid activity. When given orally, maximum effect on the blood pressure and pulse rate is achieved in 4 to 6 weeks. Other side effects are less delayed. It has recently been shown that the administration of reserpine increases the excretion of a serotonin metabolite, 5-hydroxyindole acetic acid, in the urine. Possibly the depressor action of the drug is in some way related to the depletion of serotonin in the central nervous system, since a metabolic inhibitor of serotonin has been shown to possess antihypertensive properties very similar to those of reserpine (Wilkins, 1956).

The maximum depressor and bradycrotic effect of rauwolfia may occur at any time from 2 to 8 weeks after institution of standard doses of the drug. When once established, the depressor action can be maintained by doses one third of those required to initiate the effect. In these respects the action of the

drug resembles digitalis and it might be proper to coin the words "reserpinization" and a "maintenance dose" of reserpine. The tranquilizing, fatigue-producing, and mood-depressing activities of rauwolfia appear within a day or so after treatment is started. The effect of the drug on nasal congestion, gastrointestinal activity, and appetite changes occurs within a few hours. Advantage may be taken of this fact by planning a dosage schedule that will minimize the side actions without interfering with the effects on the blood pressure. Thus, some patients prefer to take the total daily dose at bedtime so that the immediate side effects will be less prominent during waking hours; others, who find their sleep affected, choose to take the medication in the daytime. Since the depressor effect of reserpine is gradual and relatively undramatic, it is difficult to prove in an individual case that the effect is more than might occur with sedation alone. However, careful studies have shown that blood pressure depression is greater with reserpine than with sedation and for the majority of patients the side effects of reserpine are less disturbing than those with comparable doses of a barbiturate.

The administration of 2.5 to 5 mg. of reserpine intravenously or intramuscularly produces a blood pressure reduction in 30 to 60 minutes. A flush occasionally develops, somnolence is apparent, and moderate bradycardia occurs. Maximum depressor effects occur within 3 to 4 hours. Such a reduction in blood pressure may be maintained by repeated injections, but marked sedation and mood depression also occur.

The type of rauwolfia compound used in the treatment of hypertension does not appear to be important provided an adequate dosage is used. Most investigators agree that there is no difference in the side effects of the pure alkaloid, reserpine, the crude mixtures, or the alseroxylon or rescinnamine derivatives. Because the ability to standardize these preparations by biological methods is not so precise, the use of the chemically pure ingredient, reserpine, is preferred.

ORAL DOSAGE PROGRAMS

The reserpinization program consists of the administration of 0.25 mg. of the drug 3 to 4 times daily for a period of 8 weeks

with a review of progress at 2-week intervals. If side effects are not prominent and the pulse or blood pressure do not fall by the end of the fourth week, the dosage may be increased to 2.0 mg. per day. On the other hand, if side effects are unpleasant, the dose may be reduced or the time of administration altered. Reserpine may be combined with Pyronil (Sandril with Pyronil-Lilly) to reduce nasal congestion. Chlorothiazide 0.5 Gm. two or three times daily may also be prescribed. In any event, the treatment regimen should be continued for the 8-week period if possible. At this time the over-all effect of the treatment on the blood pressure and pulse rate is reviewed. All patients should experience some reduction in the pulse rate if they have received adequate doses of reserpine. When doses sufficient to produce bradycardia are given, a blood pressure reduction can be expected to occur in about 50 per cent of the patients after the eighth week of treatment. If this reduction fails to appear it is not likely that an effect on the blood pressure will be obtained with larger doses or after a longer period of treatment.

The attempt at control of the blood pressure should be abandoned in patients who have shown a poor response. On the other hand, if a definite reduction in blood pressure has been achieved, this may be maintained with few side effects by reducing the dose of reserpine to 0.25 mg. or less per day. The therapeutic effectiveness of rauwolfia drugs may also be tested by treatment withdrawal. When a blood pressure rise occurs after stopping the administration of reserpine it is probable that the drug had produced an effect on the blood pressure distinct from any psychotherapeutic effect of the regimen itself. Thus, careful observation of the effects of treatment withdrawal has the double advantage of satisfying the physician that the treatment is effective and graphically demonstrating to the patient that any expense or disability resulting from treatment has been rewarded by a significant blood pressure reduction. Because of the prolonged effect of reserpine, a period of 6 to 8 weeks must elapse after treatment is stopped before the blood pressure may be expected to rise to the pretreatment level. If after this period the blood pressure does not appear to rise, one should be careful to avoid the assumption that the remission is permanent. Since the treatment cannot be expected to have

cured the disease, the patient remains susceptible to the risk of relapse. He should remain on a regular follow-up regimen despite an apparently satisfactory reduction of the blood pressure. This point deserves special emphasis because serious complications of hypertension often occur one or two years after a patient has been discharged from treatment as apparently "cured." The following case history from the University of Michigan Hypertension Clinic illustrates the danger of assuming a permanent remission.

Case History

A 33-year-old man was referred to the Hypertension Clinic because of a history of syncopal spells at work together with an elevated blood pressure. Examination disclosed a blood pressure of 195/118 mm. Hg, but no other evidence of hypertensive complications. He was treated with reserpine over a period of three months and experienced a decline in blood pressure to 160/108 mm. Hg. It was decided to omit the reserpine for a while, but the patient failed to return for follow-up observations because he felt much improved. He was seen three months later when the blood pressure had risen to 218/130 mm. Hg. Reserpine was again prescribed, but before full effects had been achieved he was brought to the emergency clinic of the hospital because his wife had been unable to arouse him. The blood pressure was 210/132 mm. Hg on this occasion but he recovered spontaneously. On continued large doses of reserpine, the blood pressure finally fell to 172/102 mm. Hg.

Comment. This hypertensive patient was subject to attacks of syncope associated with considerable elevation of the blood pressure. The case is cited chiefly to demonstrate how easily the withdrawal of suppressive treatment can result in relapse if careful supervision is not maintained. In this case withdrawal was advised for purposes of observation only. The rise in blood pressure was unrecognized by the patient until an encephalopathic episode recurred. From this experience one may imagine that a disastrous relapse might easily occur when the hypertensive patient or his physician discontinues treatment without providing for adequate follow-up observations.

In other cases the blood pressure has remained depressed for 2 to 6 weeks after withdrawal of reserpine but severe hypertension has subsequently recurred. The only way to protect against such a relapse is to assume that the disease is never spontaneously cured and to insist on frequent examination of any patient in whom drug treatment has been withdrawn for one reason or another.

PARENTERAL TREATMENT WITH RESERPINE

The technique for treatment of the acute emergency with reserpine is outlined in Appendix 6, p. 277, and its use has been discussed elsewhere (p. 185). With such management it is not unusual for excessive blood pressure levels to return to the usual values for the patient within a few hours The symptoms of the hypertensive crisis are commonly relieved by the restoration of such "usual" levels of blood pressure. Extreme hypotension does not follow parenteral administration of reserpine to hypertensive subjects; it is, therefore, a safe drug to use both in the home and in the hospital, since it is not necessary to monitor the blood pressure carefully after the injection. The lethargy and somnolence produced by these large doses may interfere with evaluation of the clinical status. For this reason it is not advisable to continue such treatment for long periods of time. Repeated parenteral doses of reserpine should be given only when necessary to maintain the blood pressure below a predetermined level, which is usually set at or near the minimum reached after the first dose of the drug. In this way, as the effects of hospitalization on the blood pressure begin to be established the total daily requirement of reserpine is correspondingly reduced and may finally be omitted.

SIDE EFFECTS OF RESERPINE

If the patient is unusually susceptible to the pharmacologic effects of the rauwolfia alkaloids, it may be necessary to discontinue their use. Thus the nasal congesting action may lead to nasal obstruction or hemorrhage, and this may only partially be prevented by an antihistaminic agent such as Pyronil. The gastrointestinal side effects may lead to activation of gallbladder dis-

orders or peptic ulcer. While these conditions are not a definite contraindication, caution should be used in prescribing the drug for patients with a history of ulcer or gallbladder disease. The *appetite-stimulating effects may lead to progressive obesity in a* patient who is supposed to lose weight. The fluid and salt retention that occasionally follows reserpine administration is theoretically harmful in cardiac disease. If the drug is used in this condition, careful reduction of the salt intake and close attention to the salt and water balance is necessary. Perhaps for this reason reserpine has not been of particular benefit to cardiac patients. The tremor of Parkinson's disease has been produced by the drug in individuals receiving very much greater doses than customary in the treatment of hypertension. In some cases a tremor has developed on prolonged parenteral use of the drug, but in our clinic no such finding has followed conventional oral dosage even in patients with a pre-existing Parkinsonian tremor. Perhaps akin to this side effect is the occasional development of the "restless legs" syndrome. Skin eruptions have been extremely rare. Cardiac effects of the drug include reduction of the pulse rate by 10 to 20 beats per minute but atropine does not restore it to normal, suggesting that the bradycardia is not of peripheral vagal origin. Ventricular premature beats have occasionally been observed following the drug (Wilson, 1955). Fatigue is a prominent effect in many patients and often constitutes a valid reason for omitting treatment.

A small proportion of patients treated with rauwolfia alkaloids react with extreme hypotension to various conventional anesthetics and preanesthetic medications (Coakley, 1956). The cause of this sensitivity is not known, but in some instances it has been necessary to postpone surgery when it has not been possible to restore blood pressure to adequate levels with vasopressor drugs. For this reason, some anesthetists prefer that the drug be withdrawn a week or more before elective surgery is performed.

EFFECT OF RESERPINE ON MENTAL STATUS

Mental depression and apathy are the most serious sequelae of rauwolfia treatment. Agitation or apathetic depression may occur shortly after the initiation of treatment or may be delayed by

months or years. In the latter instance it appears that the depression is largely brought about by the action of some precipitating external circumstance to which the unaffected personality would be able to respond normally. This may be the explanation of the occasional suicides following use of the drug To protect against this serious outcome of treatment, the patient and his relatives are warned that depression may occur at any time during treatment. If depressive features appear, treatment should be discontinued for at least 4 to 6 weeks, only after this period can it be concluded that the depression has no connection with the medication. Should potentially depressing personal events occur while a patient is taking reserpine, it would probably be well for the treatment to be discontinued for a period of several weeks.

Apathy and loss of ambition rather than depression may develop. This more subtle effect of prolonged treatment is described in the following case history.

Case History

A 42-year-old business executive returned to the University of Michigan Hypertension Clinic 5 months after an unsuccessful sympathectomy had been performed for hypertension of 5 years' duration. The retinal arteries showed marked focal constriction; the heart was found to be considerably enlarged on percussion and on x-ray examination, but no other abnormalities were discovered. The blood pressure was 200/130 mm. Hg. With pentolinium and reserpine therapy a systolic blood pressure of 140 to 160 mm. Hg was recorded by the patient during the succeeding 6 months, but he experienced considerable malaise and constipation. A planned withdrawal of pentolinium led to an elevation of blood pressure to 234/118 mm. Hg. Chlorisondamine was prescribed, and the blood pressure in the standing position was reduced to the range of 150/98 mm. Hg for the following 6 months. During this time the patient showed his usual cheerfulness at office visits but it was learned that he had gradually withdrawn from his business responsibilities and had undertaken unremunerative part-time employment. The wife commented that during this period her husband had seemed apathetic, dis-

interested in business affairs, and unable to keep up with competition. The reserpine was discontinued without an appreciable rise in blood pressure. On a later visit the wife reported considerable improvement in her husband's attitude and initiative.

COMMENT. This patient's blood pressure was effectively controlled by a treatment program combining ganglion-blocking agents and reserpine. The change in attitude toward his work and the gradual deterioration into apathy and disinterest came so slowly that only the wife appeared to notice that an unusual change in the patient's behavior had taken place. The slow disintegration in this man's personality and attitudes was probably related to the prolonged use of reserpine, which apparently had little effect in controlling the blood pressure. In cases in which personality changes are evident, one must always consider the possibility that reserpine may produce or aggravate these disorders.

An occasional patient given small doses of reserpine responds immediately with agitation and anxiety rather than by the more common depressive pattern. Sometimes a reduction in conventional dosage will permit one to by-pass this side effect and to secure a satisfactory blood pressure reduction. Wide variations in individual responsiveness to the drug are observed. Should the conventional dosage give rise to abnormal reactions, it is always possible to proceed with very small doses. At times a good blood pressure reduction has been secured by such a program but close supervision is very necessary. It has been said that reserpine frequently unmasks innate tendencies to depression or anxiety. While this may occasionally be true, it is nevertheless possible with careful supervision to treat patients successfully who have in the past experienced some form of depression or anxiety state.

ADVANTAGES OF RESERPINE AS A SINGLE ANTIHYPERTENSIVE DRUG

In view of the many side effects and the very moderate blood pressure reductions achieved, one may well inquire why reserpine is used at all in an antihypertensive program. However,

only about one third of the patients complain of substantial interference with normal feelings of well-being during initiation of reserpine treatment. When dosage is reduced to the maintenance level of 0.25 mg. or less per day the frequency of side effects becomes negligible. Serious depressions or suicidal reactions have been avoided in our clinic by constant alertness to the possibility of their occurrence and by the willingness to suspend treatment when there is doubt concerning the patient's mental reaction to the drug. Rauwolfia compounds have an unusually beneficial effect on the hypertensive patient, since they reduce not only the standing but also the recumbent blood pressure readings. The action is unique in that it is continuously effective and less dependent on individual dosage than any other antihypertensive agent. For this reason rauwolfia is more acceptable to the patient and less likely to be abandoned in a long term program for blood pressure control in mild or moderately severe hypertension.

RAUWOLFIA MIXTURES AND COMBINATIONS

The only useful fixed combination is that with the antihistaminic agent, Pyronil, which acts to reduce the nasal congestive action of reserpine without adding to its soporific effect. This preparation is marketed as Sandril with Pyronil-Lilly The use of Ritalin to counteract the sedative or depressive features of reserpine may also be helpful. Ritalin alone has definite excitatory properties in some individuals, whereas in others little effect is manifested by standard doses. It does not appear to have any pressor activity. The combination of rauwolfia and chlorothiazide may prove useful, since neither drug requires precise regulation of the dosage. However, it would be preferable for the physician to establish the necessity and effectiveness of combined treatment by the use of each drug separately before prescribing any fixed combination of these two agents.

A number of other mixtures containing reserpine have been recommended in medical advertising. They should not be used, despite their apparent convenience, since most antihypertensive drugs that might be combined with reserpine have a precise optimum dosage, which varies widely from patient to patient. There is no advantage in prescribing more rauwolfia than is nec-

essary simply to achieve a dose of some other drug sufficient for blood pressure reduction. Flexibility in dosage schedules must be maintained.

The simultaneous use of several drugs in the treatment of hypertension is widely advocated. However, the effect on the blood pressure of adding rauwolfia to hydralazine or to ganglion-blocking agents is no more than an additive one. The side effects of each drug also appear. While it is true that some side effects cancel each other out (for example, there is less constipation when rauwolfia is used in combination with ganglion-blocking agents and less tachycardia when it is used in association with hydralazine), additional side effects also make their appearance. If a combination of drugs is used in the treatment of hypertension, each drug should be evaluated separately for its effects on the blood pressure and used in combinations only when it can be shown in each patient to improve the control of his blood pressure.

The combination of rauwolfia with mecamylamine or other ganglion-blocking agent is reserved for those patients whose response to ganglion blockade alone is associated with marked constipation or with wide fluctuations in blood pressure. Since the advent of chlorothiazide, these deficiencies in response to ganglion blockade are seen so infrequently that rauwolfia drugs are rarely necessary. If the regimen is satisfactory, rauwolfia compounds are never added. If control leaves much to be desired, either because of wide blood pressure fluctuation, excessive orthostatic gradient, or severe constipation and rauwolfia is to be added to the regimen, it is prescribed after the previous dosage has been sufficiently stabilized to determine the effectiveness of adding reserpine. Two months later a re-evaluation is carried out and the combined treatment program is continued only if a further blood pressure reduction appears to have followed the use of rauwolfia and is not associated with added side effects. Considerably less than one third of the hypertensive patients in the University of Michigan Clinic continue to take combinations that include rauwolfia.

When reserpine has been discontinued a notable decrease in the complaint of fatigue and lethargy has often been observed without any loss of effective blood pressure reduction. The case

history quoted on p. 203 is an example of this experience. The deterioration in the personality of this patient was a high price to pay for the questionable added value of reserpine.

The use of rauwolfia in combination with veratrum alkaloids does not cancel out the disagreeable side effects of veratrum and adds little to the very difficult problem of dosage adjustment. The blood pressure reduction that is reported with most drug mixtures is probably due largely to the rauwolfia content. Since reserpine does not potentiate the effects of hydralazine, one would not expect the combination to be superior to reserpine alone; effective blood pressure reduction with the usual dose of hydralazine alone is not often achieved. It must be admitted that this is a personal impression and that in many clinics this combination is a mainstay of treatment For this reason, the combination program as outlined by Dr. Freis is included in Appendix 12, p. 309, for those who wish to try this regimen.



CHAPTER 21



Mecamylamine and Other Ganglion-Blocking Agents

In the preceding chapters we have identified those patients for whom ganglion-blocking agents would seem advisable to prevent progression of the disease and to prolong survival. In Appendix 7, p. 279, Appendix 11, p. 300, and Appendix 12, p. 309 precise details of dosage schedules are given. The following discussion concerns the theoretical aspects on which these recommendations are based. The discussion will center largely around mecamylamine; the place of the other blocking agents will be discussed later.

HEMODYNAMIC EFFECTS OF GANGLION BLOCKADE

The effect of ganglion-blocking agents on the circulation has been extensively studied. In the hypertensive subject, the chief effect of such a blockade on the circulation is to reduce cardiac output (Crumpton, 1955). This effect has been attributed to inhibition of tonic sympathetic discharge to the heart (Beck, 1958) and to a failing venous return (Smith, 1956a). Certainly the greater decline in orthostatic blood pressure than in the recumbent reading is related to this effect on the venous return.

There is some difference of opinion as to how much reduction

in recumbent blood pressure can be achieved by treatment with ganglion-blocking agents. In the University of Michigan Hypertension Clinic, the effects on the blood pressure are almost entirely limited to reductions in the readings obtained in the standing or sitting position (Cottier, 1957). Other clinical investigators have reported some reductions in recumbent blood pressure as well (Freis, 1956a; Moyer, 1956, 1957). Such differences in the reported results of treatment may arise from the fact that a greater reduction in standing blood pressure is deliberately produced by these clinicians. This may lead to a more substantial reduction in the recumbent reading or perhaps to a "resetting" of the carotid sinus barostat (McCubbin, 1958). On the other hand, the difference in reported results may simply be the result of overestimation of the initial "control" recumbent blood pressure as recorded in the pretreatment periods In any event, it is generally agreed that it is difficult to achieve a prolonged reduction of the recumbent blood pressure to normal values by treatment with ganglion-blocking agents alone, if the patient is to be able to walk about without syncope.

Experimental observations suggest that the hemodynamic effect of mecamylamine, which has a somewhat different chemical structure from the other quaternary compounds, is nevertheless similar to the more completely studied drugs. One observation (Cottier, 1957) indicates that mecamylamine reduces cardiac output in the sitting position much as was observed with other ganglion-blocking drugs used in a previous similar study (Smith, 1956a). Reductions in renal blood flow and glomerular filtration rate and increases in the retention of salt and water seem to be of equal magnitude whether the hypertensive patient is treated with mecamylamine or with quaternary blocking agents (Ford, 1956). The effects of this drug on the peripheral circulation have been studied only by Freis (1956a), who has made the surprising observation that, in contrast to the effects of quaternary blocking agents, the skin temperature gradients between the central and peripheral parts of the body are not abolished by mecamylamine, nor are reflex digital vasoconstrictor responses prevented. Increases in the digital blood flow are not so great as with comparable depressor doses of hexamethonium. The explanation of these significant results is not clear.

ADVANTAGES OF MECAMYLAMINE

Mecamylamine, or Inversine, is superior to previously developed quaternary ammonium blocking agents. The major advantage in clinical practice is that the drug is totally absorbed in the gastrointestinal tract, so that a given oral dose has a reasonably predictable effect. With the quaternary compounds, from 5 to 25 per cent of the ingested dose is estimated to be absorbed, and this rate of absorption appears to vary from day to day and *to depend on peristaltic activity and other unknown factors.* Mecamylamine also differs from these other drugs in that only a portion of each dose is removed by the kidney, whereas the quaternary blocking agents are totally dependent on renal excretion for removal from the body.* These differences are apparent when patients with renal excretory failure are treated with ganglion-blocking agents. The dose of mecamylamine necessary to reduce the blood pressure in such individuals is usually only slightly less than in patients with good renal function. In contrast, the dose of quaternary ammonium compounds must be greatly reduced in the presence of renal excretory insufficiency. Furthermore, when glomerular filtration is suppressed by excessive hypotension, the quaternary compounds are eliminated from the body with difficulty and thus the hypotensive effects may be greatly prolonged. Another advantage of mecamylamine lies in the fact that the patients receiving this drug do not develop tolerance to the medication. In contrast, for most quaternary compounds, especially hexamethonium and pentolinium, the dosage must be increased over the first several months of treatment in order to maintain the depressor action. If the medication is withheld for a week or more, sensitivity may be restored and readjustment of dosage is again necessary when the drug is recommenced. With mecamylamine the optimum dosage can be *reached in a few weeks and the requirement does not* usually increase thereafter. Furthermore, withdrawal of mecamylamine does not lead to increased sensitivity to the action of this drug

* It has recently been demonstrated that increased pH of urine and body fluids decreases renal elimination and increases intracellular localization and depressor action of mecamylamine (Milne, 1957). This effect is probably of little clinical importance in the day-to-day management of patients with mecamylamine except when major acidifying or alkalinizing regimens are simultaneously prescribed.

(Cottier, 1957). Another advantage of mecamylamine is that it has a more gradual onset and offset of action. Even when it is given parenterally, blood pressure reduction does not occur for 30 or 40 minutes. Since the effects appear more slowly, blood pressure reduction is never abrupt as with the quaternary compounds. The timing of dosage is correspondingly less critical and the general effect on the patient more satisfactory. After several months of treatment with mecamylamine, it may take a week or more for all evidence of ganglion blockade to disappear. Perhaps because it possesses a different chemical configuration, mecamylamine has been shown to have a larger volume of distribution in the body than the quaternary ammonium compounds that enter only the extracellular fluid space. It is presumed that some intracellular penetration of mecamylamine occurs and may account for the prolonged effect described above (Milne, 1957).

The autonomic blocking effects of mecamylamine are remarkably similar to those of other ganglion-blocking agents. Equal degrees of blockade of the sympathetic and parasympathetic nervous system are attained by all ganglion-blocking drugs, as judged by the appearance of dry mouth, decreased perspiration, constipation, and impotence. In general all are blocked to an equal extent at the same level of orthostatic hypotension. However, there are some exceptions: pupillary dilation is more prominent with chlorisondamine while constipation and dry mouth are less frequent and severe when trimethidinium is prescribed.

MANAGEMENT OF THE SIDE EFFECTS OF MECAMYLAMINE

Because of the predictable absorption of mecamylamine, the side effects do not vary greatly from day to day. On the other hand, they are persistent because of the slow offset of action of the drug. The biggest difficulty arises from the constipation and flatulence caused by inhibition of upper gastrointestinal motility. Abdominal distention may cause pressure on the diaphragm, and this in turn may produce a sense of dyspnea. Prevention of the constipating effects of mecamylamine has proved difficult. The gastrointestinal tract should be stimulated by laxatives just before treatment is started. After a while, bowel move-

ments may improve so that cathartics are needed less often. The choice of laxative will vary from patient to patient, but some drug in this category must be prescribed daily in order to produce a steady stimulating effect on the bowel. If simple measures such as fruit juices, milk of magnesia, and mineral oil fail to be effective, 32 to 65 mg. of cascara may be used. Phenolphthalein cathartics which have stimulating effects on the small bowel may be useful. In the more difficult cases, a daily dose of one or two tablets of Alophen* has been found successful. Oral pilocarpine is more expensive and usually less effective. Because the only serious risk from mecamylamine therapy is the production of ileus, laxatives should be used daily for the first several weeks of treatment and the dose or strength of the cathartic should be increased if there is no bowel movement. After 48 hours of bowel inactivity, mecamylamine should be withheld temporarily, but after an evacuation has occurred, the drug treatment should promptly be resumed in order to prevent a serious hypertensive "rebound." When a suitable daily laxative dose has been determined, it must be taken indefinitely or until the patient finds by trial and error that the laxative is not necessary to offset the inhibiting effects of mecamylamine on the bowel. A method to combat constipation has been described with great detail in Appendix 7, p. 279, because improper management of the constipating action of ganglion-blocking agents is the chief reason that physicians and patients abandon the use of these drugs before they have been given a fair trial. When chlorothiazide is prescribed in combination with mecamylamine as recommended in Appendix 7, p. 285, most patients secure a satisfactory reduction of the orthostatic blood pressure without major gastrointestinal disturbance. In rare individuals who continue to have severe constipation, the additional use of reserpine may prove helpful or treatment with trimethidinium may be substituted. The other side effects of ganglion-blockade are managed with difficulty. Dry mouth and dry skin are particularly troublesome. Visual effects are most marked in the young person but may be partially relieved with glasses. Impotence is common; cautious treatment withdrawal for 12 to 24 hours usually

* Alophen is a Parke-Davis preparation which contains aloin, extract of belladonna, powdered ipecac, and phenolphthalein.

restores potency, but more prolonged withdrawal of a ganglion-blocking agent is dangerous. Postural dizziness is related to control of the blood pressure and will be discussed below. The concomitant use of chlorothiazide has so reduced the amount of mecamylamine necessary for blood pressure control that the side effects of the treatment regimen are now much more acceptable to the patient than they were formerly.

CONTROL OF THE BLOOD PRESSURE DURING THE ADMINISTRATION OF GANGLION-BLOCKING DRUGS

In Appendix 7, p. 278, the details of an effective treatment program using various ganglion-blocking agents is outlined. Very few patients will ever experience orthostatic syncope if one establishes the therapeutic goal that morning and evening standing (not sitting) systolic blood pressure is kept at 150 mm. Hg. While this is admittedly an incomplete reduction of the blood pressure, it is not likely to lead to the frequent complaint of postural dizziness. When the patient has become used to the regimen, it may be possible to experiment with further reduction in the orthostatic blood pressure level. In some cases in the Hypertension Clinic at the University of Michigan, it has been possible to maintain systolic standing blood pressure levels as low as 110 to 120 mm. Hg without difficulty. On such a program, however, orthostatic syncope is likely to occur occasionally, especially in the early morning hours This complaint is apt to be experienced by men while shaving in the morning and by women while working in the kitchen in the early morning. In some subjects there is a further distinct fall in blood pressure after meals.

Since orally administered mecamylamine has a delay in onset and offset of action and a total time span of orthostatic blood pressure reduction lasting 6 to 8 hours or more, it is possible to achieve reasonably effective blood pressure control by twice-daily doses. If this is successful, it is a great added convenience to the patient, since the medication can be taken at home in the morning and evening just after the determination of the blood pressure. In patients who require more than 10 mg. twice daily the addition of a noonday dose is recommended for more prolonged and smoother effect. In those individuals in

whom the blood pressure shows a greater than normal decline at the noon hour when peak action is expected, there may be advantages in a schedule of 4 equal daily doses.

It is to be expected that the morning dose will have its maximum effect at about noon and that the effect will be waning by dinner when the medication is next taken. This latter dose in turn will have some effect on the sitting or standing blood pressure during the evening but the effect by morning will be negligible. On awakening, however, sympathetic tone is at its minimum and some postural effects may persist. The morning dose again increases the degree of blockade while vasomotor tone itself increases through the day. Blood pressure records taken in the morning on arising and before dinner in the evening probably are the least likely to show the maximum orthostatic benefit from the drug action. This is another reason why the relatively elevated standing systolic blood pressure of 150 mm. Hg at these times may be optimal, since the blood pressure taken at noon or just before going to bed is often so much lower as to come near to producing postural syncope. It may also be the reason that some patients complain of orthostatic dizziness or weakness at the lunch hour or at bedtime. When blood pressure is recorded at such times the explanation of these symptoms becomes evident.

REGULATION OF TREATMENT BY DETERMINATION OF BLOOD PRESSURE IN THE HOME

At first it was difficult to become convinced of the necessity for the patient to determine his own blood pressure and to regulate his antihypertensive program accordingly. Not only would this unconventional approach cause inconvenience and extra expense, but it was thought that the blood pressure cuff might serve to increase the patient's anxiety and actually to aggravate his disease. Furthermore, with the shorter-acting ganglion-blocking agents, frequent blood pressure readings each day would have been necessary to evaluate accurately the effects of treatment.

This feeling, together with an antipathy to the use of ganglion-blocking agents, is apparently shared by a large number of in-

ternists and physicians dealing with hypertensive disease. A questionnaire submitted to a randomly selected group of such individuals in March, 1956, showed that at least half did not use ganglion-blocking agents frequently in the treatment of hypertension, and of those who did, fewer than 50 per cent made an effort to have the patient control his treatment by taking his own blood pressure (Hoobler, 1957a). Comments written on the questionnaires that were returned led to the impression that for reasons of inconvenience, special expense, or fear of the production of an anxiety reaction, home recording of blood pressures was not generally advised even for cases of severe hypertensive disease. In contrast, many clinics dealing especially with the problem of hypertension have instructed most patients with severe forms of this disease in the technique of taking their own blood pressure. Corcoran (1955) and Fries (1956) have stressed the great value of these blood pressure readings in securing optimum control of the disease. When this technique was tried in the Hypertension Clinic of the University of Michigan, the value of the procedure in the management of the severely hypertensive patient quickly became apparent. The frequency with which home blood pressures could be taken was an advantage since it was possible to arrive at a truer estimate of the extent of the hypertension than when one relied on the random office blood pressure readings alone to direct treatment. It was found that office readings varied from visit to visit, while home records showed a remarkably consistent effect of treatment on the blood pressure. Not only was it useful to know the usual blood pressure of the patient from day to day, but it was helpful in his management to know the reading at the time various symptoms occurred that might have been caused by either overdosage or underdosage of medication. Apparent treatment failures with mecamylamine, based on the evidence obtained from office readings only, were often shown to be erroneous. The patients themselves were pleased with the evident daily control of the blood pressure and the occasional carefully supervised treatment withdrawals demonstrated to them that the suppressive therapy was effective and necessary for control of the disease. With this program, the patient could be accepted as a real partner in the program of long-range control and with the many readings available

between office visits it became possible to supervise the management of the disease on the basis of the usual blood pressure reading in the home rather than on the basis of casual office readings.

When we became convinced of its value, efforts were made to simplify the procedure so that it would cause the least possible inconvenience. As a result the program for supervision of the blood pressure by the patient, as described in Appendix 7, p. 278, has been developed. The essential features are that the blood pressures are determined at home and only in the morning and evening prior to taking the medication. Only one reading is recorded, the systolic, because both systolic and diastolic levels and lying, sitting, and standing determinations are interdependent and cannot be individually altered. Accordingly, the patient is asked to record only the systolic readings and in the standing position, because this demonstrates the maximum depressor effect of the medication that can be tolerated without rendering the patient liable to orthostatic syncope. In order to reduce the patient's dependence on others, a blood pressure cuff* has been devised that permits the patient to take his own readings. This relatively inexpensive device is designed to permit him to slide a conventional cuff on his arm and tighten it like a bracelet. By holding the pressure gauge in one hand and compressing the inflating bulb with the other, he can inflate the cuff above the systolic level. He then puts the stethescope in his ears and connects the tubing to an end-piece built into the cuff itself. As the pressure in the cuff is allowed to fall by adjusting the needle valve, the Korotkoff sounds are easily identified by the patient and the blood pressure read off the dial held in the left hand. The procedure can easily be carried out by any patient after a little practice (Fig. 1). The accuracy of the method has been established by a critical comparative study (Blaquier, 1957).

Contrary to the opinion that this program might decrease the importance of consultations between patient and physician, visits to the clinic are now far more productive, since one can go over daily records of the blood pressure, discuss symptoms and side effects, and plan with the patient the best possible management

* The instrument is marketed by the Propper Manufacturing Company, 10–34 44th Drive, Long Island City, N.Y., as the "Autosfig." See Figure 1, opposite.



Fig 1 Use of the Autosfig in self-determination of the blood pressure (Reprinted from Blaquier, P, and Hoobler, S W *Univ Michigan M Bull* 23, 356, 1957)

based on accurate day-to-day registration of the blood pressure. Patients under this form of control are conscientious and reliable in co-operating with the physician, and the general results have been most gratifying. Because of the almost universal feeling among physicians that it was not good psychology for patients to record their own blood pressure an evaluation of this aspect of the program was performed by Dr. Jack Westman, a member of the Neuropsychiatric Department of the University of Michigan Hospital (Westman, 1958). The study revealed that of 13 patients interviewed before they knew that they were to take their own blood pressure and again several months later, only four were ultimately dissatisfied with the plan of recording the blood pressure in the home. Two of these were unhappy because the blood pressure had not been lowered by treatment The remaining two, who had experienced satisfactory blood pressure reductions, were at the initial interview anxious and timid concerning the procedure and did not wholeheartedly co-operate. Despite effective blood pressure reduction they did not desire to continue supervision of their own readings.

From these observations it may be concluded that the program will be accepted only by patients who are willing and unafraid of the prospect of taking their own blood pressures and who are properly instructed in the use of the instrument. Other patients may have regular blood pressure supervision by other methods such as increasing the frequency of office visits or enlisting the aid of a nurse at a nearby clinic or at the patient's place of employment.

If readings in the home fail to show a satisfactory reduction of the blood pressure, the patient will be dissatisfied. There is, of course, no way in advance to guarantee success or failure of the control program. If care is taken to explain to the patient that failure of treatment does not necessarily mean immediate disaster, particularly in cases where the initiation of a treatment has been elective, it should be possible to avoid dissatisfaction. The importance of a satisfactory and confident relationship between the patient and his physician is again emphasized. Advance consideration of possible failure to lower the blood pressure and a frank discussion of the proposed technique of treatment is advisable It is wise to set a relatively minor reduction of ortho-

static blood pressure as an initial goal, since in almost all patients such a change in blood pressure can be secured. This will avoid initial disappointment and permit the setting of a progressively lower level if the regimen is well tolerated. Such a program gives the patient the satisfaction of tangible advancement as he sees successive goals for reduction achieved without side effects that are too disabling.

USE OF GANGLION-BLOCKING AGENTS OTHER THAN MECAMYLAMINE

Conversion to another ganglion-blocking agent may be advisable when mecamylamine results in the production of tremors or confusion, or when it does not appear to be well tolerated. In this case the drug of choice would be trimethidinium (Ostensin). This medication may be started at a level of 20 mg. three times daily and the total dose increased by 60 mg. daily until blood pressure control is secured (see Appendix 7, p. 278). The drug has the advantage of producing less constipation and dry mouth than mecamylamine does, but it has the disadvantage of being only partially absorbed by the oral route and having a weaker ganglion-blocking action. Excretion is reduced and the effectiveness of small doses increased in cases of renal insufficiency.

An equally useful alternate drug is chlorisondamine (Ecolid). This drug should be given in dosages of 25 mg. twice daily with increases of 25 mg. per dose as necessary to achieve blood pressure control. It is important with this drug, as with all quaternary ganglion-blocking agents, that control of bowel activity be maintained, since constipation will lead to a greater percentage of absorption of the administered dose of the drug. With Ecolid, marked dilation of the pupils may affect vision enough to interfere with the occupation of some patients. This can be partially corrected by the use of 1 per cent pilocarpine eyedrops. Some of the effects are due to the admission of too much light to the retina; to relieve this dark glasses may be helpful (Smith, 1956).

An alternate treatment regimen may be centered on pentolinium tartrate administered three times daily in approximately equal divided doses. Visual effects are less prominent, but otherwise the effects of this drug resemble those of chlorisondamine. The dosage starts at 25 mg. three times daily but is usually in-

creased rapidly to a dosage level of 150 to 200 mg. three times daily (Agrest, 1954).

CONDITIONS ALTERING SENSITIVITY TO GANGLION-BLOCKADE

The physician who uses ganglion-blocking drugs will frequently recognize situations that create an unusual sensitivity or refractoriness to a dose of the drug that has previously been effective in managing the blood pressure. These effects largely relate to variations in available circulating blood volume, to vascular tone, and to extracellular fluid accumulation. Edema and fluid retention, as in cardiac failure, may cause refractoriness, whereas dehydration following hemorrhage, vomiting, diuretics, or excessive sweating on hot days will lead to a sensitization to the regular dose of the ganglion-blocking agent. It may be supposed that these latter conditions all decrease blood volume and cause a contraction of the venous reservoir with heightened neurogenic venous tone as a result. When this increase in venous tone is canceled by ganglion blockade, the veins dilate and blood becomes pooled in them. Venous return to the heart declines, cardiac output falls to a greater extent, and a pronounced reduction of the blood pressure results.

This mechanism is the probable explanation of the adjuvant action of chlorothiazide (Weller, 1959). Treatment with this drug usually withdraws several hundred milliliters of plasma volume and a greater amount of extracellular water with electrolytes The sensitizing effect appears within 12 to 24 hours after starting treatment and can apparently be maintained indefinitely, while desensitization may occur with equal promptness on treatment withdrawal. Changes in blood pressure in patients taking ganglion-blocking drugs closely follow the effect of the diuretic, so that chlorothiazide must be continuously administered for maximum effectiveness and serious hypertensive rebounds may occur soon after chlorothiazide is omitted.

The opening up of many unused blood channels with a corresponding reduction in peripheral resistance may also accentuate the effects of ganglion blockade. This is seen when large volumes of blood are diverted into the splanchnic circulation following a heavy meal, ingestion of alcohol, or violent exercise.

Patients receiving large doses of ganglion-blocking agents should not engage in heavy physical work. Dyspnea, dizziness, and palpitation may accompany the hypotension created by such diversion of the circulating blood.

Spontaneous daily fluctuations in neural tone to vascular smooth muscle must be invoked to explain the diurnal variations in blood pressure that occur despite a relatively continuous degree of ganglion blockade. Just as in "idiopathic" postural hypotension the recumbent position decreases the circulatory adaptability to the upright posture, so also in the patient under the influence of ganglion blockade, recumbency reduces postural reflexes. Consequently, postural hypotension is more prominent in the early morning hours than later in the day. Autonomic activity undoubtedly increases with the day's activity, thus partially counteracting the blockade by evening.* Furthermore, autonomic excitation easily breaks through chemical blockade in stressful situations. In addition release of epinephrine will easily nullify hypotensive drug effects since the effect of epinephrine is magnified when the sympathetic nervous system has been partially blocked. In these various ways one may explain the common clinical observation that, despite a constant mecamylamine effect, the orthostatic blood pressure is lower in the morning than in the evening and that the blood pressure may quickly rise in the physician's office or under conditions of unusual stress.

Infections, especially those caused by gram-negative organisms and by the viruses of the common cold and influenza, may lower the blood pressure of a hypertensive patient to normal even without the added effect of medication. It is not surprising to find that following such illnesses patients who are taking ganglion-blocking agents may become so hypotensive at their usual dose level that they are hardly able to rise from bed. They must of course omit or reduce temporarily such medication in this situation. Surgery, by the same ill-defined "toxic" action, may also intensify the effects of ganglion blockade. Furthermore, since blood loss is poorly tolerated by a patient whose sympathetic nervous system responses are reduced, ganglion-blocking drugs should be discontinued for 12 to 24 hours before surgery and

* If it may be accepted that extracellular tissue pressure is a factor in maintaining vascular tone, it might be argued that morning sensitivity to ganglion blockade follows a loss of tissue fluid from the legs during recumbency.

reinstituted cautiously thereafter. Such contraindications are of course only relative, since these drugs have also been used successfully for the deliberate creation of hypotension during anesthesia to avoid the risk of arterial bleeding.

PARENTERAL USE OF GANGLION-BLOCKING AGENTS

The use of rapidly effective programs to lower the blood pressure has been summarized in the chapter on the treatment of hypertensive emergencies (p 184), and the details and management are presented in Appendix 5, p. 270. Blood pressure control may be secured rapidly by parenteral administration of a ganglion-blocking agent of the quaternary variety, but this procedure must be attended with careful blood pressure supervision. Reduced levels in the recumbent position can be maintained effectively for a week or more, after which only orthostatic hypotensive effects are usually apparent The reason for the development of the phenomenon of toleration is not clearly explained It may be postulated that after prolonged blockade in the recumbent position a reduction in cardiac output no longer occurs, perhaps because of the development of refractoriness to ganglion blockade, or because compensatory increases in circulating plasma and extracellular volume lead to a decrease in venous tone. It is interesting to note that if devices are applied to the body which create a negative pressure and thus draw blood into the veins, blood pressure reduction in the recumbent position can be intensified (Restall, 1952).

In the initial choice of ganglion-blocking agents to be used parenterally, one usually selects at the onset of the program a short-acting agent such as hexamethonium. If the reduction is attended by satisfactory improvement and it is the desire to continue such management, the dosage may be converted to a longer acting parenterally administered agent such as pentolinium or chlorisondamine. These quaternary blocking compounds have less effect on gastrointestinal motility than when they are given orally, perhaps because of the different route of absorption. In the rare instance when oral therapy appears to fail because of serious gastrointestinal side effects, the long-term use of these drugs by the parenteral route may prove effective.



CHAPTER 22



Other Methods for the Treatment of Hypertension

This chapter will be concerned with regimens that are sometimes effective and should be applied to patients with hypertension. The surgical treatment of hypertension will be discussed. Other effective drugs and a few drug combinations that have been reported to be advantageous will also be reviewed.

PSYCHOTHERAPY

All would agree with the importance of psychotherapy in the management of the patient with hypertension, particularly in the early stages of the disease. Few would adopt the same approach to the problem. To tell the patient who has mild hypertension to "forget about his blood pressure" or "don't have it taken again" may be good psychotherapy but it is poor preventive medicine. On the other hand, too great insistence on the importance of the blood pressure alone, which has so far been the theme of this book, might justifiably be condemned as too mechanistic an approach. Intelligent psychotherapy requires a frank discussion with the patient, with emphasis on the hopeful aspects of his case and on the ability of the physician to prevent or arrest the development of complications. It does not seem wise to conceal the blood pressure reading from the patient or to answer a direct question evasively, since the essence of good

psychotherapy is to establish mutual confidence and understanding.

After a discussion of the patient's prognosis and the program that is to be inaugurated for his protection, attention should be directed toward tension-creating influences in his environment. Some situations in which the patient may be placed are not susceptible to alteration, toward these a philosophical attitude must be encouraged. The questions posed by hypertensive patients are often difficult to answer. For example, would a divorce greatly lower the blood pressure or improve the prognosis? Will the retirement of an active executive postpone the later complications of hypertensive disease by relieving the tension in which he lives? Should an ambitious young man with early hypertension accept an opportunity for advancement even though such promotion would require a longer working day, increased responsibilities, and considerably more stress? These questions must be answered by the individual patient. In most cases the perfect solution of all personal difficulties would not cure the hypertension or render it innocuous. Consequently, one should be cautious in recommending that an important decision be based on the hope that somehow a change in the way of life would permanently lower the blood pressure. Less extensive changes in the patient's personal environment are, however, strongly recommended when they may lead to less tension in daily living. More important, perhaps, is to change the attitude of the hypertensive patient toward the world around him. He should be impressed with the importance of reducing compulsive traits and perfectionistic attitudes, restricting the number of responsibilities he accepts, and living a generally more relaxed life and at a slower pace.

Certain daily routines are helpful. If possible, an hour of complete relaxation in the middle of the day is advised. It is not unusual to see the blood pressure fall 40 to 50 mm. Hg in the systolic range and 20 to 30 mm. in the diastolic reading during a 30-minute period of quiet resting in the clinic. After this common experience is demonstrated to the patient by showing him the effect of the rest period on his blood pressure, it is then explained that midday relaxation would permit him to start the afternoon with a considerably lower blood pressure reading than if he had continued throughout the day without a rest. Further-



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pone the development of left ventricular failure. Opinion is divided concerning the efficacy of salt restriction in lowering the blood pressure. The experience of most investigators tends to confirm that of Corcoran, Taylor, and Page (1951), who reported that approximately 20 per cent of patients placed on a 200 mg. sodium diet demonstrated some moderate degree of reduction in blood pressure. However, the ability of the patient to remain indefinitely on such a restricted diet was limited. By combining chlorothiazide and salt restriction, a more effective and more acceptable "desalting" program has been made available. Because of the saluretic action of chlorothiazide, this regimen does not require extreme salt restriction; but the addition of extra salt at the table or in cooking tends to nullify its effects. Such a "desalting" treatment is to be favored for patients with mild hypertension and for the arteriosclerotic subject in whom mild hypertension may be associated with headaches, edema, or other complications for which blood pressure reduction might provide relief If cardiac manifestations such as congestive failure appear in the hypertensive subject, more potent drugs may be necessary, but the continued value of salt restriction and chlorothiazide cannot be denied.

Whether the rice diet of Kempner (Newborg and Kempner, 1955) depends for its efficacy on sodium restriction or some other factor is still an open question. Most authors believe that sodium restriction is the significant element, but it should be remembered that the diet is also restricted in protein and fat and that on this regimen serum cholesterol falls strikingly. Thus other factors than sodium chloride restriction may be involved in the unquestionably dramatic effect of this diet in some patients with severe forms of hypertensive disease. In general, however, the rice diet fails because the patient abandons treatment before it can help him. In the severely ill patient, the time spent in attempting control of the blood pressure by a rice diet would be better used in applying immediately effective forms of treatment that the patient will find more acceptable for permanent suppression of the hypertension.

Restriction of dietary protein is useful in the treatment of renal failure, but reduction of protein intake to the level at which protein balance is maintained is not likely to have an effect on the

blood pressure in established hypertension. Restriction of dietary fat and cholesterol is probably indicated in every American male in middle life; and in hypertension this restriction may be even more important because of the accelerated rate of atherogenesis associated with an elevated blood pressure. It is not practical, however, to insist on too many food restrictions in a disease as long-lasting as hypertension. Therefore, until more is known about the precise type of dietary fat that should be restricted to prevent atherosclerotic arterial disease, the patient with hypertension should not have this added dietary problem superimposed on the many already placed in the way of normal living

SYMPATHECTOMY

Among the most impressive "cures" of hypertension in the years prior to drug treatment have been those that occasionally followed sympathectomy. Such dramatic results appeared in approximately 10 per cent of individuals. Another 20 to 30 per cent have experienced statistically significant blood pressure reduction up to the end of the first postoperative year (Hoobler, 1951). Blood pressure reduction persisting beyond the first year is likely to remain reduced in at least the majority of patients (Hoobler, 1950a) and survival is prolonged (Smithwick, 1956). Furthermore, sympathectomy appears to render the blood pressure more sensitive to ganglion-blocking agents (Brown, 1948) or to chlorothiazide (Weller, 1959), so that if the operation is a failure in terms of blood pressure reduction, it frequently permits the previously unsuccessful diuretic or ganglion-blocking agent to work without disabling side effects.

Sympathectomy has the single great advantage over chemotherapy that it does not require continued co-operation on the part of the patient after the operation. When the operative procedure brings a continued reduction in blood pressure, the result is most gratifying to doctor and patient; in contrast, failure of the blood pressure to fall is most disappointing, particularly if a postoperative disability remains. It is impossible to predict in advance which patient is likely to experience a favorable result, and therefore acceptance of the operation involves the gamble that a good result will follow. Since the combination of chloro-

thiazide and mecamylamine provides as effective a reduction in blood pressure in a higher proportion of cases without involving operative risk or postoperative disability, it is not surprising that sympathectomy is rarely advised at present in the management of hypertension.

However, sympathectomy might be considered for the treatment of the same types of hypertension as those for which ganglion-blocking agents are recommended. Thus while the operation is elective in a case of severe established hypertension without complications, it may be strongly recommended in patients with severe hypertension associated with cerebrovascular complications or a malignant exacerbation of their disease. When mild azotemia is present, ganglion-blocking agents may still be tried, but sympathectomy has not proved successful With this exception, however, over a wide range of hypertensive disease, the choice between chemotherapy and surgical treatment may be presented to the patient.

Many hypertensive individuals have been referred to the University Hospital for sympathectomy because the side effects of ganglion-blocking agents were found to be intolerable or the blood pressure did not appear to be substantially reduced by these drugs. A good proportion of such patients who are instructed to keep a record of their own blood pressure at home and who are placed on the meticulous program outlined in the Appendix can be shown to respond to treatment and to tolerate the side effects of mecamylamine. Sympathectomy should not be recommended simply because drug treatment is alleged to have failed in the hands of another physician. On the other hand, if a very carefully supervised trial causes truly unacceptable side effects or the patient objects to taking drugs and will not remain consistently under suppressive therapy, sympathectomy may be the best treatment for him.

It may be asked whether a patient whose blood pressure has proved refractory to a sympathetic blocking drug is a proper candidate for surgical sympathectomy. It may be supposed that those hypertensive subjects who are likely to have a good surgical result are so easily managed by small doses of ganglion-blocking drugs that the question of surgery never arises. There has been insufficient experience with sympathectomy since the advent of

blood pressure in established hypertension. Restriction of dietary fat and cholesterol is probably indicated in every American male in middle life; and in hypertension this restriction may be even more important because of the accelerated rate of atherogenesis associated with an elevated blood pressure. It is not practical, however, to insist on too many food restrictions in a disease as long-lasting as hypertension. Therefore, until more is known about the precise type of dietary fat that should be restricted to prevent atherosclerotic arterial disease, the patient with hypertension should not have this added dietary problem superimposed on the many already placed in the way of normal living

SYMPATHECTOMY

Among the most impressive "cures" of hypertension in the years prior to drug treatment have been those that occasionally followed sympathectomy. Such dramatic results appeared in approximately 10 per cent of individuals. Another 20 to 30 per cent have experienced statistically significant blood pressure reduction up to the end of the first postoperative year (Hoobler, 1951). Blood pressure reduction persisting beyond the first year is likely to remain reduced in at least the majority of patients (Hoobler, 1950a) and survival is prolonged (Smithwick, 1956). Furthermore, sympathectomy appears to render the blood pressure more sensitive to ganglion-blocking agents (Brown, 1948) or to chlorothiazide (Weller, 1959), so that if the operation is a failure in terms of blood pressure reduction, it frequently permits the previously unsuccessful diuretic or ganglion-blocking agent to work without disabling side effects.

Sympathectomy has the single great advantage over chemotherapy that it does not require continued co-operation on the part of the patient after the operation. When the operative procedure brings a continued reduction in blood pressure, the result is most gratifying to doctor and patient; in contrast, failure of the blood pressure to fall is most disappointing, particularly if a postoperative disability remains. It is impossible to predict in advance which patient is likely to experience a favorable result, and therefore acceptance of the operation involves the gamble that a good result will follow. Since the combination of chloro-

cumbent position cannot be completely averted by an apparently successful program of drug treatment. A third distinct argument in favor of surgical treatment has appeared since the advent of chlorothiazide. Sympathectomy appears to render the hypertensive patient sensitive to the effects of this diuretic drug. Thus in two patients with the same blood pressure levels, one with and one without sympathectomy, the former subject might easily experience a reduction in blood pressure to normal levels following the administration of chlorothiazide whereas this would be most unusual in the patient who had not undergone operation The blood pressure reduction achieved by addition of chlorothiazide is asymptomatic and well tolerated. The potentiating effect of sympathectomy seems to last almost indefinitely since we have found patients who have undergone sympathectomy many years before who are still responsive to chlorothiazide administration (Weller, 1959). Sympathectomized patients who have been required to take ganglion-blocking agents for several years to keep their blood pressure under control may exhibit such sensitivity to chlorothiazide as to permit omission of all ganglion-blocking agents and emancipation from their side effects. In many other splanchnicectomized patients with residual hypertension the degree of additional ganglion blockade necessary for control has become negligible in terms of side effects when chlorothiazide has been administered From this preliminary experience, it may be predicted that if one were to sympathectomize all severely hypertensive patients and then to treat them with chlorothiazide the frequency of satisfactory and asymptomatic blood pressure reduction would exceed 50 per cent. Certainly such an increase in the probability of a good result from sympathectomy should encourage the more frequent use of this procedure in the treatment of hypertension.

Occupational and personal considerations often make surgical sympathectomy the method of choice. It is not advisable to administer ganglion-blocking agents to patients whose occupation necessarily involves the health of others, such as elevator operators, bus and truck drivers, and those who manipulate heavy equipment. Sympathectomy may also be recommended for patients whose occupation involves a great deal of activity or movement from place to place as, for example, with business

executives, traveling salesmen, and professional people. When by temperament it is apparent that an individual is unable or unwilling to settle down to a careful suppressive program for his condition and to use drugs indefinitely to control the blood pressure, surgical treatment may deserve a first choice. However, the drug regimen and the blood pressure supervision that has been outlined in the Appendix has deliberately been simplified to make it acceptable to any patient who observes reasonably regular hours of work and has some intelligence and emotional stability. In point of fact many of the most co-operative and successfully treated patients are those who were originally thought too impatient or unintelligent for such a program. The executive type of person whose energy and drive have led him to a commanding position in his occupation is frequently the type of individual who understands and follows the plan of management outlined in this book with maximum effectiveness. By contrast, in the unreliable patient who for various reasons comprehends poorly the purposes and side effects of suppressive treatment, sympathectomy is favored as the initial choice for treatment, for if he is indeed severely hypertensive the only prospect of successful management lies in trying for a "cure" or alleviation of the disease during the brief time that he will submit to medical supervision.

Under certain circumstances sympathectomy is contraindicated in an otherwise suitable case. This is exemplified by the obese patient in whom operation is technically difficult and often unsatisfactory. When a program of drug treatment is outlined for such a patient every effort is made to encourage weight reduction at the same time, so that if the treatment is unsatisfactory, the possibility of relief by sympathectomy will not be denied to him. Hypertensive patients with pulmonary disease and thoracic spinal disease such as kyphosis and scoliosis are also excluded from surgery for technical reasons. General experience has taught that patients over the age of 55 and with terminal complications of hypertension including extensive myocardial infarction, hemiplegia, and azotemia are poor candidates. However, a recent coronary thrombosis from which recovery has been complete is not a contraindication, nor is a history of congestive failure, provided the patient is in good compensation at the time of the in-

tended operation. Two to three months after recovery from a cerebrovascular episode, the risk of further extension of the cerebral lesion during surgery is reduced sufficiently to make operation safe. In fact, because recurrence of this lesion depends so much on whether the blood pressure is satisfactorily and continuously reduced, such a history should be viewed as favorable to the possibility of performing sympathectomy (Pierson, 1957).

A relative contraindication to sympathectomy exists in patients with peptic ulcer. Following operation they seem to have a higher frequency of gastrointestinal hemorrhage or perforation of the ulcer, perhaps because interruption of the afferent sympathetic nerve pathways reduces visceral pain and prevents adequate symptomatic warning of ulcer recurrence. Reflex constriction of vessels to a bleeding ulcer may also be abolished by the denervation. These are probably the reasons for the prolonged and serious episodes of bleeding and the occasional sudden perforations which occur after sympathectomy in the patient with hypertension who has had a previous history of peptic ulcer. While a splanchnicectomy may still be performed on patients who urgently need such treatment for their hypertension, chemotherapy is certainly preferable as the first choice in planning for control of the blood pressure.

While it is extremely difficult to compare the different sympathectomy procedures in terms of the postoperative result to be expected, Table 12 presents for each type of operation the probable frequency of prolonged reduction in blood pressure (not necessarily "cure") as measured by approximately the same criteria. It will be seen that the greater the extent of sympathectomy, the more frequently is a good result obtained However, with the more extensive surgery the operative time and risk and the postoperative disability are correspondingly increased. At the University of Michigan Hospital the maximum sympathetic denervation possible with a one-stage procedure is preferred. The operation devised by Dr. Max Peet of supradiaphragmatic sympathectomy and ganglionectomy can be performed in one stage and is less likely to lead to disabling orthostatic hypotension, since the lumbar sympathetic outflow is not removed. The results of this procedure have been improved by extending the operation upward to include the fifth and sixth sympathetic

TABLE 12. REPORTED EFFECT OF VARIOUS FORMS OF SYMPATHECTOMY ON THE BLOOD PRESSURE IN HYPERTENSION

Authors	*Extent of ganglionectomy*	*No cases reported*	*Follow-up (years)*	*"Good" results*	*Definition of "good" result*
Grimson, 1949	Stellate through L-1 or L-2	113	1–8	% 66	Comparable pre- and postoperative data for each patient not presented Median reduction in diastolic readings of all patients exceeded 20 mm. Hg at 1 year and appeared sustained in subsequent years. Deaths included
Evans and Bartels, 1949	D-3 or 4 through L-1	173	½–3	47	Casual diastolic blood pressure fell more than 20 mm. Hg and to less than 120 mm. in "good result" cases.
Smithwick, 1948	D-8 through L-1	439	1–5	37	Postoperative blood pressure fell 20 mm. Hg or more below resting preoperative diastolic blood pressure. Deaths included.
Hammarstrom, 1947	D-8 through D-12 D-8 through L-1 or 2	25 55	½–6½	42 59	Mean of 24 hourly diastolic blood pressure readings in hospital reduced more than 25 mm. Deaths included. More extensive sympathectomy improved results in males particularly.
Peet, Woods, Braden, 1940	D-8, 9 or 10 through D-12	202	9–18 mos	18–44	Casual diastolic blood pressure declined more than 25 mm. Hg in 18%, more than 15 mm. in 44%, deaths included.
Hoobler, 1951	D-6, 7, 8 or 9 through D-12 (D-6 through D-12)	338 (54)	10–16 mos.	29 (50)	Casual diastolic blood pressure reduced more than 20 mm. Hg. Deaths included.

Reprinted from Hoobler, S. W., Manning, J. T., Paine, W. G., McClellan, S. G., Helcher, P. O, Renfert, H., Peet, M. M., and Kahn, E. A.: The Effects of Splanchnicectomy on the Blood Pressure in Hypertension. A Controlled Study. *Circulation* 4, 173, 1951.

ganglia bilaterally (Kahn, 1954). The extended sympathectomy is achieved without adding to the time of hospitalization or duration of surgery by the removal of two ribs on each side instead of one. This maneuver provides a better exposure and has the incidental advantage of requiring less traction on the remaining ribs and thus perhaps of reducing the frequency of postoperative intercostal neuritis, an uncommon but distressing form of postoperative disability.

ADRENALECTOMY

When cortisone became available, two clinical groups began to perform adrenalectomy for the treatment of hypertensive disease. The results leave little doubt that some adrenal function is necessary to maintain hypertension, but in the opinion of most investigators a clinical "cure" can only be achieved by keeping the patient in a state of marginal adrenal insufficiency. In such a condition, the patient is subject to sudden and swift adrenal failure when exposed to infection or other forms of stress. Because of the pre-existing vascular disease and the necessity to limit replacement treatment, hypertensive patients subjected to a total adrenalectomy are more vulnerable to a sudden and fatal bout of adrenal insufficiency than patients who undergo total adrenalectomy for other reasons. Furthermore, the studies reported by Thorn's group (1952) indicate that the operation is not helpful in patients with serious renal excretory failure but is beneficial chiefly in cases in which cardiac failure and salt and water retention are prominent. Since one can usually control the cardiac manifestations of hypertension with drug management while the control of renal excretory failure in this disease is troublesome, adrenalectomy appears to offer few advantages where it is most needed.

The Philadelphia group have approached the problem of adrenalectomy somewhat differently. Their latest procedure involves combining a Smithwick type sympathectomy with a unilateral adrenalectomy (Zintel, 1955). If this procedure does not bring about an effective reduction in blood pressure, the remaining adrenal gland is submitted to total or subtotal excision at a later operation. Whether this represents a net improvement

in the surgical management of hypertensive disease must await the collection of further statistics concerning the frequency of postoperative death from adrenal insufficiency, over a substantial time interval. However, they have demonstrated that sympathectomy is not without benefit in serious forms of hypertensive disease and by adding a unilateral adrenalectomy they have gone one step further toward preparing for an alternative surgical procedure that might be used with comparative ease if the initial operation were unsuccessful. It is unfortunate that this rational program for surgical treatment could not have undergone further development and trial before an equally effective method of medical management took its place.

HYDRALAZINE

The use of hydralazine as a single antihypertensive drug was popularized by the group of investigators at the Cleveland Clinic (Taylor, 1952). The drug was supposed to act by inhibiting the release of a centrally originated humoral substance, but subsequent investigations suggest that it also has a direct vasodilator action. Cardiac output, renal blood flow, and peripheral blood flow are definitely increased by hydralazine and the same is probably true of the splanchnic vascular bed. The net effect on the blood pressure represents the summation of the decrease in peripheral resistance and the increase in cardiac output. As would be expected, the diastolic blood pressure falls, pulse pressure widens, and tachycardia is observed. The skin is flushed and signs of increased circulation appear as in hyperthyroidism and after injection of histamine. The drug also has an antihistaminase action that may cause edema, urticaria, joint pains, and a syndrome suggesting serum sickness.

While improvement in renal blood flow would seem to be a beneficial effect, glomerular filtration rate is not increased and azotemia is not reduced by treatment. Therefore any benefit to be derived from renal vasodilatation must be based on the theoretical grounds that renal vasoconstriction initiates or maintains hypertension. Careful serial studies of the effects of prolonged oral doses of the drug on blood pressure and renal blood flow reveal that tolerance appears after the passage of several weeks

so that the renal hyperemia, undoubtedly present in the initial phases of treatment, disappears after prolonged treatment (Vanderkolk, 1954). The extent of renal vasodilatation that was observed on initial testing had no relation to the magnitude of the immediate or subsequent reduction in blood pressure. Consequently it is unlikely that this drug, when it is effective in reducing blood pressure, acts by counteracting renal vasoconstriction. On the other hand, the pharmacologic actions of hydralazine carry the disadvantages that increases in the cardiac output may result in the production of heart failure or the worsening of angina pectoris, the histamine-like actions of the drug may lead to gastric hemorrhage or exacerbation of peptic ulceration or to the production of edema

Despite these deficiencies, many clinics dealing with hypertension use hydralazine extensively. Patients soon come to tolerate the early side effects, and a very gradual increase in dosage permits one to achieve finally the recommended level of 100 to 200 mg. 4 times daily. In reports of the Cleveland Clinic group, the blood pressure was substantially reduced in over half of the individuals receiving such treatment (Taylor, 1952). The program currently used at the Cleveland Clinic has been submitted to the author through the courtesy of Dr. Harriet Dustan and is recorded in Appendix 9, p. 294. In a less extensive experience in the use of this drug at the University of Michigan Hypertension Clinic, reductions in blood pressure have not been commonly observed (Vanderkolk, 1954).

The use of large doses of hydralazine for a year or more has led to the occurrence of a syndrome resembling lupus erythematosus with low-grade fever, joint pain, and an eruption on the face associated with the development of typical lupus erythematosus cells in the peripheral blood, an abnormal protein pattern, and a positive cephalin cholesterol flocculation test (Perry, 1954; Dustan, 1954). Withdrawal of treatment was followed by a spontaneous remission, although on occasion it was necessary to administer cortisone. When the syndrome developed, the blood pressure had usually fallen dramatically but after treatment withdrawal it rose again. The frequency of the development of this complication bears some relationship to the dosage of hydralazine. Few cases have been reported in which a dose of less

than 50 mg. 4 times daily has been given. It is possible that the discrepancy in the observations in different clinics on the efficacy of hydralazine in reducing the blood pressure may be explained by the longer duration and greater dosage used by those who report favorable results. Reduction in blood pressure perhaps represents an early preclinical manifestation of "hydralazine disease." If this were the case, treatment such as we have employed is too little and too brief in nature and would not lead to a reduction in blood pressure.

The frequently advocated use of hydralazine in combination with other antihypertensive drugs deserves some mention at this point. The combination of hydralazine with rauwolfia has been discussed in the chapter on rauwolfia treatment (p. 207). The combination with a ganglion-blocking agent has also been presented elsewhere (p. 299).

VERATRUM COMPOUNDS

Veratrum alkaloids have had a long and interesting history in medicine. Veratrum has been used to create an after-discharge following nerve stimulation in the isolated frog hind limb. It is likely that this same effect occurring at a critical concentration level causes repetitive discharges of the afferent fibers leading from the carotid sinus and coronary artery receptors to the central nervous system, where they link with centers in the brain stem affecting vasomotor control. The fact that the blood pressure can be lowered in every hypertensive patient when this theoretical threshold is reached illustrates that no hypertension is truly irreversible and that if a way could be found to maintain increased afferent receptor discharge, all forms of hypertension could be normalized. Unfortunately, the critical threshold for intensification of autonomic afferent activity occurs only slightly below the point at which these same stimuli to the nodose ganglion and central vagal connections give rise to emesis. Consequently, while depressor effects can be achieved by critical intravenous dosage, emesis occurs if the rate of administration exceeds the rate of degradation or removal of the veratrum alkaloid. When an effective dose, given orally or parenterally, does not at first lead to vomiting, the sensitivity of the emetic center

seems to undergo a progressive increase so that after a period of time emesis occurs at a concentration threshold not greatly above that for vasodepression.

The net result is that while blood pressure reduction may always be produced, the emetic effects of the veratrum alkaloid become more and more prominent as time passes. To attempt to avoid this sensitization effect, a single daily dosage regimen was designed (Hoobler, 1952). It was hoped that by allowing for daily excretion of the drug the increasing emetic effect might be avoided. This plan proved partially successful and for a number of months severely hypertensive patients could be carried on such a regimen with only occasional bouts of nausea and vomiting for which they were well prepared, since they came at approximately the same time each day. This dosage program is summarized in Appendix 8, p. 290 It is not routinely recommended at the present time, since more effective control with fewer side effects can be achieved with mecamylamine and chlorothiazide.

Nevertheless, veratrum compounds possess some advantages over other antihypertensive drugs. Clinical responsiveness is not related to renal function. Blood pressure reduction occurs in the recumbent as well as in the upright position, so that orthostatic syncope is not common. The bradycrotic and the inotropic effect of veratrum on the myocardium may be useful in hypertensive cardiac failure. In toxemia of pregnancy, one may achieve an effective blood pressure reduction without the risk to the fetus that may occur when a quaternary ammonium compound is administered In the patient with severe hypertension or impending hypertensive crisis who is known to be refractory to ganglion-blocking agents, the reflex arc activated by veratrum remains available and blood pressure reduction can be achieved in a matter of minutes Finally when blood pressure reduction is mandatory and the side effects of ganglion-blocking agents have resulted in the development of a serious or dangerous type of ileus, the use of veratrum may bring about a temporary blood pressure reduction without producing further parasympathetic inhibition. Veratrum alkaloids, despite their potent action on the circulation and on the heart, have been remarkably free of clinical risk. Large overdoses accidentally ingested have been without disas-

trous effect. Unusual cardiac arrhythmias occasionally are induced and the production of complete heart block has been observed. However, fatal intoxication has not developed and the fact that all the cardiac effects can be abolished by the intravenous administration of one milligram of atropine sulphate provides for effective control of disturbances of cardiac rhythm.

Many efforts have been made to get around the emetic properties of these agents. It was hoped that protoveratrine would prove less emetic than other purified veratrum derivatives. Although there may be inert alkaloids in the whole extract of veratrum viride that provoke emesis more readily when these crude extracts are administered, most of the purified derivatives on the market have an equal depressor-to-emetic ratio as tested clinically and it would appear that further improvement by extraction of different components will not prove successful. No support can be found for the claim that any agent derived from veratrum has an improved ratio over the mixture of protoveratrine A and B. It has recently been discovered that while both protoveratrine A and B are active intravenously, only protoveratrine A is absorbed readily from the gastrointestinal tract. When very large doses of protoveratrine B are given by mouth, a slower depressor effect is observed, but other side effects ensue (Winer, 1956).

The threshold effect of veratrum alkaloids must be emphasized. Until the blood and tissue levels reach a critical concentration, no effect on the blood pressure is observed. When this concentration is exceeded by as little as 10 to 20 per cent, for a substantial period, emesis also occurs. Many drug mixtures or combination programs use such small doses of veratrum as to result in blood concentrations well below the effective threshold for depressor action. Furthermore, it has not been shown in any critical experiment that an ineffective concentration of veratrum might lower the threshold or magnify the depressor effect of any other antihypertensive drug. Until such drug synergism is demonstrated, the use of subthreshold doses of veratrum in drug mixtures, or combinations would appear to be irrational. Despite such theoretical objections, a number of clinical investigators have used veratrum in combination with other drugs and have claimed an added measure of antihypertensive effect. We have

had little experience with such combined programs preferring to depend on an effective dose of veratrum alone for blood pressure reduction.

DIHYDROGENATED ERGOT ALKALOIDS

It has long been known that ergotoxin will block the vasoconstrictor effects of epinephrine in isolated preparations. Because ergotoxin has direct smooth muscle constricting properties of its own, it has been contraindicated in hypertension and vascular disease generally. A series of chemical investigations in Switzerland resulted in the synthesis of a series of dihydrogenated ergot compounds in which the vasoconstrictor action of the parent substance was abolished but the adrenergic-blocking effect preserved. Parenteral administration of this drug to patients with hypertension results in an interesting series of physiologic events The pulse slows, the blood pressure falls moderately, blood flow to the extremities increases, and nasal stuffiness develops. An occasional side effect is nausea, vomiting, or fatigue. The blood pressure reduction is not as dramatic nor as predictable as with veratrum or ganglion-blocking compounds. The drug is well tolerated except for the nasal stuffiness The response to a standard dose is somewhat unpredictable and it has been our impression that on repeated parenteral administration increasingly less effect was observed.

Even more disappointing is the effect of oral administration of the drug. Only minor blood pressure reductions are obtained when the conditions of trial are carefully standardized. Responses tend to wane and even the nasal congestive effects wear off after several weeks of treatment. To obtain modest blood pressure reduction it is necessary to resort to parenteral dosage. The most effective program devised by the Swiss investigators for using the mixed ergot alkaloids in the treatment of hypertension is summarized in Appendix 10, p. 297. This precise therapeutic program has not been employed in our clinic. Random observation of the responses of the blood pressure to injected doses comparable to those recommended has not shown impressive results, and when control of even mild hypertension by oral medication has been attempted, no measurable success was achieved. The

evidence quoted by Kappert (1949) that the drug has a curative effect in hypertension because after treatment withdrawal the blood pressure no longer rises may also be interpreted to mean that the original blood pressure reduction was a psychotherapeutic effect that persisted after treatment withdrawal. It is hard to be convinced that the use of this agent for several months could result in a continued blood pressure reduction for many further months after treatment was stopped. The suppressive treatment of hypertension, to be proved effective, should be accompanied by a rise in blood pressure when placebo treatment is substituted.

DIBENAMINE DERIVATIVES

The pharmacology of dibenamine and dibenzyline has been reviewed by Nickerson (1949). These exceedingly interesting compounds apparently combine irreversibly with the receptor sites for the vasoconstrictor (excitatory) actions of epinephrine and norepinephrine. The inhibitory actions of epinephrine are not blocked; these include vasodilation and the production of tachycardia. After the intravenous infusion of dibenzyline (1 mg. per kilogram of body weight or more) sympathetic (adrenergic) nerve activity is substantially inhibited (Woodward, 1952). The combination with the vascular receptors is unusually prompt since it may occur immediately following intra-arterial administration of dibenzyline (Duff, 1957). Recovery of a vasoconstrictor response to sympathetic stimulation or epinephrine release after such a combination requires several days. It might be supposed that at such a level of adrenergic blockade the recumbent depressor effects would be more prominent than with ganglion-blocking agents. Such is not the case. Furthermore, tolerance develops even to the orthostatic hypotensive effects, so that this drug is of little use in prolonged management (Corcoran, 1952).

From a practical standpoint the use of dibenzyline has been unsuccessful in the treatment of hypertension, not only because of the rapid development of tolerance but also because the drug fails to block the cardiac sympathetic efferent response to orthostatic or emotional stimulation. Even the orthostatic hypotension produced initially by dibenzyline is rendered inacceptable to the

patient because of the intense reflex tachycardia that accompanies it. The drug has another peculiar side effect that is a marked sense of fatigue even when small doses are prescribed. Parenteral or oral dibenzyline will certainly reduce the blood pressure in a patient whose hypertension is due to pheochromocytoma and it may be a useful agent in managing the malignant and inoperable forms of this condition Its use as a sole antihypertensive agent has been unsuccessful in the competent hands of the investigators at the Cleveland Clinic, and a short experience at the University of Michigan Hypertension Clinic has confirmed their observations.

The drug is marketed in combination with rauwolfia and veratrum under the name "Miopressin." There is no evidence of a synergistic effect of dibenzyline with either of these antihypertensive drugs. In the recommended dosage the veratrum can have little effect. It is probable that what therapeutic action this mixture may possess lies in the rauwolfia component.

THIOCYANATES

For many years thiocyanates were recognized to be the only chemical agents that could effectively lower the blood pressure. Even before more potent drugs were available, the side effects of goiter production, skin eruptions, and occasional serious psychotic responses, particularly when blood levels of this compound exceeded 10 mg. per cent, led to its gradual abandonment. Mild reduction of blood pressure was evident in some controlled studies (Ruskin, 1947), and its parenteral use to relieve hypertensive headaches has more recently been described (St. Pierre, 1953). The mode of action of the drug has never been established despite the careful studies of the Chicago investigators (Davis, 1951). It is not used at present for the treatment of hypertension.

NITRATES, NITRITES, AND OTHER DIRECT VASODILATORS

It would seem that an agent acting directly upon arteriolar smooth muscle to decrease peripheral resistance would be the

ideal drug for the treatment of hypertension. It is, therefore, surprising that some direct-acting compound has not been developed that would be effective. Despite considerable research it has not been possible to synthesize a substance that delivers nitrite into the circulation at a sufficiently slow, steady, and stable rate to maintain adequate vasodilation for blood pressure reduction. Nicotinic acid, pentaerythrol tetranitrate, sodium azide, and various forms of long-acting nitrites and nitrates have been recommended for treatment of hypertension, but none has successfully passed critical testing. Efforts to reduce blood pressure by parenteral administration of direct vasodilators have included the use of sodium nitroprusside intravenously, an agent that is effective in surprisingly small dosage and with a considerable margin of safety (Page, 1955) (see Appendix 5, p. 267).

PYROGENS

The history of the use of pyrogens as antihypertensive agents is an extremely interesting one. When it was discovered that the normal kidney had a protective action against the development of experimental hypertension, efforts were made to extract from renal tissue enzymes or other substances that would relieve experimental hypertension or cure its human counterpart. These relatively crude extracts of hog kidney, when administered to malignant hypertensive patients by Page and collaborators, produced a marked depression in blood pressure and improvement in the malignant hypertensive state (Page, 1941). Unfortunately, this therapy was associated with frequent reactions and with low-grade fever. When the hypothetical depressor substance resisted further purification and separation, it was finally concluded that a nonspecific pyrogenic protein was the effective depressor agent. Reduction of the blood pressure of the Goldblatt hypertensive dog by an endogenous depressor substance released from a turpentine-induced abscess was noted by Stamler and associates (1950), and contamination with a pyrogenic substance of inulin infused for the measurement of glomerular filtration rate caused dramatic blood pressure reductions with increases in renal blood flow (Goldring, 1944). Meanwhile clinicians became increasingly aware that bacterial endotoxins of certain

species not only could lower the blood pressure in hypertension but could produce shock in normotensive individuals. A relatively purified bacterial pyrogen, marketed as Pyromen, was used deliberately to produce febrile reductions in blood pressure in malignant hypertensive patients (Page, 1951). Considerable improvement occurred when the renal function of the patient was not seriously diminished.

This difficult program, which requires producing a daily fever, has been abandoned with the advent of newer and more potent antihypertensive agents, but the pronounced improvement observed further supports the contention that blood pressure reduction in itself may have considerable therapeutic value in hypertensive disease, especially in the malignant phase.

The future usefulness of these compounds is conjectural. Highly purified polysaccharide derivatives of endotoxin have now been synthesized that have such potency that a few micrograms will produce shock in the experimental animal and will presumably render a hypertensive patient normotensive. The other actions of these compounds suggest, however, that they are primarily toxic agents and it is questionable whether they can be manipulated in such a way as to reduce the blood pressure effectively without causing serious side effects.

The mode of action on the blood pressure is of interest. While in the dog hepatic venoconstriction with splanchnic pooling and reduction in cardiac output appears to be the chief mode of action, it is not clear that the same effects occur in the human being. The species variation in response to endotoxin varies widely, and further study is required.

CHAPTER 23

Retrospect and Prospect

Changed ideas and methods in the treatment of hypertensive disease have arisen so imperceptibly, and the inadequacies of current treatment are still so obvious that we little appreciate the advantages already won in the battle against this second greatest killer among cardiovascular diseases.*

In the realm of ideas we have witnessed the defeat of negative concepts that perhaps had rationalized our former helplessness. Today, sustained elevation of the blood pressure is accepted as a cause of vascular disease, and blood pressure reduction, irrespective of how it is accomplished, appears to prevent vascular deterioration and to prolong life. The rationalization that high pressure is somehow "necessary" to sustain the circulation has been abandoned. The etiology of the disease remains obscure, but all-embracing explanations are out of fashion. Today a multifactorial approach is preferred—seeking to split off from the unknown certain specific entities whose cause and cure may be recognized. For example, improvements in diagnostic methods have increased the frequency with which cases of pheochromocytoma and renal hypertension are recognized, while primary aldosteronism has recently been discovered to be a previously unidentified cause of certain cases of "essential hypertension." The possibility that a type of human hypertension is induced by re-

tention or maldistribution of sodium chloride has become more evident from current epidemiologic studies and clinical observations with chlorothiazide. We are therefore slowly approaching the day when hypertension, now designated "essential," will be classified and treated according to etiology.

Although we are still deficient in fundamental explanations, the great extension of research in the universities and pharmaceutical laboratories has led to many nonspecific ways of dealing with essential hypertension. In the last fifteen years five major advances have been achieved in the treatment of hypertensive disease: (*a*) the discovery of a technique for ganglion blockade in man, (*b*) the use of this method in long-term treatment, (*c*) the discovery for the Western World of the usefulness of rauwolfia alkaloids, (*d*) the finding of a ganglion-blocking drug that is completely absorbed from the gastrointestinal tract, and (*e*) the discovery of a nontoxic diuretic that will magnify and prolong the previously recognized benefits of dietary salt restriction in the treatment of hypertension.

With these discoveries a new era has been opened. It is now possible for any seriously motivated patient with relatively early hypertension to control his blood pressure and to postpone almost indefinitely the vascular lesion that formerly would have caused his early death. Cerebral hemorrhage and death from hypertensive heart failure should be rarely encountered even in the patient with a seriously advanced form of the disease. The mortality rates from hypertension are slowly falling across the nation as physicians use these new drugs with increasing effectiveness.

Nevertheless there are still many needless deaths, owing to poor understanding of the natural history of hypertension, the failure to recognize the necessity for its continuous suppression, and the inability or unwillingness to use the new techniques intelligently. It has been the theme of this book that the patient with milder hypertension requires indefinite supervision and perhaps simple prophylactic treatment while the severely hypertensive subject should be accepted as a full partner with the physician in a never-ending campaign for the suppressive treatment of the disease.

Reviewing the achievements of the past decade, one can surely

look forward hopefully to the future. Our greatest handicap, of course, lies in not knowing the primary causes of hypertensive disease; as basic research expands more and more, a "break-through" may be expected. On the technical side, new and improved drugs that will lower blood pressure with fewer side effects will undoubtedly become available. These will require a considerable revision of this book since the choice of when to initiate treatment of the blood pressure has required balancing the risks of hypertension against the side effects of medication. Were an effective drug made available without side effects of any kind, this author would recommend its use in everyone with a blood pressure higher than the median for his age and sex, since the evidence of the accelerating effect of sustained hypertension on vascular disease is convincing. Such a regimen applied over a lifetime might well eliminate a major portion of the thrombotic vascular accidents that our antihypertensive treatment of today cannot prevent, since such treatment is almost of necessity too little and too late. The nature of the intimal lesion of atherosclerosis suggests a long period of build-up that is hardly reversible as it enters a terminal phase. So while the mechanical accidents of hypertension can be controlled, it is impossible to prevent acceleration of the atherosclerotic lesion until we have an "ideal" antihypertensive drug that can be used from the inception of the disease.

It has been a pleasure to work during the years when the treatment of hypertensive disease has advanced from a negligible to a considerable prospect of success. The friendship of many colleagues engaged in the study of hypertension has been a rich experience. The assistance obtained from their publications is gratefully acknowledged.* Associations with the many past and present collaborators in the Hypertension Clinic have been richly rewarding. This book has presented ideas derived from all these sources. It is to be hoped that the reader will find it useful in improving his management of patients with hypertensive disease.

* Many valuable books, reports, and symposia on hypertension have recently been made available. The titles are included in the alphabetical bibliography under the following author's or editor's names. Addis, 1949; Bell, 1950, Braun-Menéndez, 1946; Dexter, 1941; Fishberg, 1954; Goldring, 1944, Hoobler, 1958, Master, 1952, Page, 1949, Page, 1956, Pickering, 1955a; Schroeder, 1953, and Smirk, 1958.

APPENDIXES

APPENDIX 1

Details of Pharmacologic Testing for Pheochromocytoma

It is necessary to secure as stable a blood pressure as possible with most tests to be described. The test procedure should, therefore, be explained to the patient first and then performed without conversational stimuli No injections are made until the blood pressure in the opposite arm returns to the basal level prior to the venipuncture. The drug is then administered evenly, with careful attention given to the time of injection recommended for each drug. Blood pressure and pulse rate are taken every thirty seconds in the opposite arm for a period of at least 5 minutes after the injection.

HISTAMINE TEST (ROTH, 1945)

PROCEDURE. Histamine acid phosphate solution is used. 0.0275 mg./ml. (= 01 mg. histamine base/ml.) is prepared fresh every month or so and stored in the refrigerator. The dilution represents 1/100th of the strength of the conventional 1:1000 solution of histamine acid phosphate used for gastric analysis. After the blood pressure has stabilized, 2.5 ml. (.025 mg. of the base) is given intravenously in 10 to 20 seconds. The blood pressure is taken every 30 seconds in the opposite arm for 5 to 10 minutes.

The usual response is a flush, vasodilator headache, and transient hypotension lasting less than 2 minutes and followed by return to normal or slightly supernormal values in the next 3 to 5 minutes. If the subsequent rise exceeds the preinjection level by 30/20 mm. Hg, pheochromocytoma is suspected. The

needle is left in the vein after the injection so that 5 mg. of Regitine may be given immediately in case of a hypertensive reaction.

CONTRAINDICATIONS. Severe hypertension, severe asthma, angina pectoris.

TETRAETHYLAMMONIUM (ETAMON) TEST (LADUE, 1948)

PROCEDURE. 200 to 300 mg. of tetraethylammonium chloride (Etamon-Parke, Davis) is given intravenously in 20 to 30 seconds after the blood pressure has become basal. The patient will notice transient paresthesias, blurring of vision, and a mild tachycardia. The systolic and diastolic blood pressure will fall 30 to 40 mm. Hg in hypertensive patients. In patients with azotemia or arteriosclerosis, more marked hypotension may occur but can be corrected promptly with a head-down tilt or intravenous administration of vasoconstrictor drugs. If the patient is over the age of 50, a dose of 200 mg. intravenously is usually sufficient for the test. A small dose of norepinephrine (5 to 10 μg.) should be available in the event of an unusual hypotensive reaction and the intravenous needle should be kept open during the test.* The side effects may last from 15 to 20 minutes. Orthostatic hypotension may persist for a longer time. After the test patients should be carefully observed for syncope when they first regain the upright posture.

Most patients with pheochromocytoma show a marked secondary rise in blood pressure after the period of hypotension. The secondary rise should exceed the preinjection blood pressure level by 20 to 30 mm. Hg. A moderate rise in blood pressure occurring normally in young persons after tetraethylammonium may be a source of error on rare occasions. The test is not as likely to be positive in cases of pheochromocytoma as is the histamine test. If an extreme pressor response occurs, the patient

* The author finds it convenient to have a solution of norepinephrine (0.2 ml. of 1:1000 solution of the base) always ready in a sterile container for immediate dilution to 20 ml. and administration. In this concentration, the norepinephrine does not lose potency and is always available for a hypotensive crisis.

should be instructed to sit up and hang his legs over the side of the bed so that the orthostatic hypotensive effects of the drug may offset the pressor effects of the secretion from the tumor.

CONTRAINDICATIONS. Cases of angina pectoris and arteriosclerosis in which severe hypotension may be precipitated.

PHENTOLAMINE (REGITINE) TEST (GIFFORD, 1952)

PROCEDURE. The drug is prepared for injection by dissolving in sterile water the contents of one ampoule containing 5 mg. of the drug powder. It is necessary to do this just before the test, since prepared solutions deteriorate on standing. The phentolamine is given intravenously over a 45-second interval. The rate of the injection must be slow and carefully timed if consistent results are to be obtained. A reduction of 25 mm. Hg in the diastolic blood pressure level in at least two successive readings is considered a positive response.

False positive reactions occur in patients under treatment with various antihypertensive drugs. They are also reported in azotemia. In the absence of any of these explanations, about 10 per cent of cases still show false positive reactions. Therefore, the Regitine test should be viewed as a screening procedure only. It should be repeated and should be checked with a benzodioxane or histamine test. False negative results are rare. It should be noted that if the diastolic blood pressure is not greatly elevated, the Regitine test cannot be positive without inducing considerable hypotension since a diastolic blood pressure fall of 25 mm. Hg is necessary to qualify as positive.

CONTRAINDICATIONS. The test should be performed cautiously and with smaller doses in patients with a history suggestive of cardiac arrhythmias or angina pectoris. The drug has cardioexcitatory properties. A mild tachycardia is regularly produced and in at least one instance in our clinic mild angina pectoris has been observed following the injection. This symptom can be relieved by vasodilators and no harm should come from it if proper precautions are taken.

BENZODIOXANE (BENODAINE) TEST (GOLDENBERG, 1947)

PROCEDURE. The drug is supplied in solution by the manufacturer. The calculated amount (0.25 mg./kg. but not to exceed 20 mg.) is injected slowly at a steady rate such that one half the dose has been administered in the first minute. Blood pressure readings taken every 30 seconds on the opposite arm are then inspected. If a rise of less than 15 to 20 mm. Hg systolic or diastolic has occurred, the remainder of the dose is given in the second minute. If such a rise has already occurred, the injection is stopped, since in all likelihood the test will be negative and further injection may only cause distressing side effects (tachycardia and dyspnea) together with a further elevation of the blood pressure. Since such a rise may occur from anxiety alone, it is important that the patient be reassured before the injection. If possible he should not know the moment the injection is started. The more elaborate testing technique of Goldenberg and Aranow (1947) was devised for this purpose but probably is not necessary if the test is performed with proper attention to details.

Any reduction of systolic and diastolic pressure exceeding 5 to 10 mm. Hg should be viewed as a positive reaction. False negative reactions occur with greater frequency than with the Regitine test. False positive reactions are said to occur in azotemia and after sedative and hypotensive drugs (Soffer, 1952).

CONTRAINDICATIONS. The drug should be given carefully in patients with extremely severe hypertension although the procedure outlined above should protect against most serious hypertensive reactions. Cardioexcitatory effects on the heart rate might theoretically be adverse in angina pectoris.

APPENDIX 2

Analysis of Urinary Catechol Amines in the Detection of Pheochromocytoma

GENERAL CONSIDERATIONS

Approximately 3 per cent of intravenously administered epinephrine or norepinephrine can be recovered in the urine by sensitive assay techniques. This recovery is further reduced if the urine is neutral or alkaline and subject to oxidation. There is a wide variation in "normal" 24-hour urine catechol amine excretion, the limits being approximately 10 to 150 μg. per 24 hours.

Many contaminants result in fluorescent end products that may affect the determination of epinephrine or norepinephrine. Certain vitamins capable of producing fluorescent end products should not be given during the urine collection nor should the patient receive pressor amines such as nasal vasoconstrictors, benzedrine, or Ritalin. Urinary epinephrine and norepinephrine cannot readily be distinguished by the method as described below. Since both are usually found in increased amounts in the urine in cases of pheochromocytoma, the inability to distinguish between them would seem to make little practical difference.

Since false positive results may occasionally occur, pharmacologic tests should also be performed where possible before a patient is advised to undergo surgical exploration In one case, where preoperative catechol amine levels were 486 and 87 μg in two successive 24-hour specimens, exploration failed to reveal a tumor in the adrenal region. In four cases of pheo-

chromocytoma examined in our clinic and subsequently confirmed at operation, the urinary excretion of catechol amines was well above the normal range.

False negative results may occur if proper precautions are not taken in the collection. During a period of normotension no elevation of urinary catechol amines may be found. In such circumstances it might be better to obtain a specimen during an attack. The patient is instructed as follows:

If you have an attack immediately drink two glasses of water and collect *all* urine in the bottle furnished you up to four hours from the time at which you previously emptied your bladder. If you cannot remember precisely when this was, void immediately, wait four hours and save for analysis the complete urine specimen voided at that time.

Normal standards for a 4-hour collection period must at present be estimated on the basis of normal values for a 24-hour period. Thus, a 4-hour sample containing in excess of 24 µg. should be considered abnormal.

COLLECTION PROCEDURE

It is important that a complete 24-hour urine specimen be collected and each portion immediately acidified to prevent oxidation of catechol amines. Fluorescent contaminants present in most stoppers must be excluded by covering them with cellophane. After the specimen is collected, an aliquot of approximately 100 ml. may be taken for chemical assay. This acidified sample may be sent through the mail or stored in the refrigerator without deteriorating. The instruction page used in our laboratory to insure the collection of a proper sample is reproduced below.

SAMPLE INSTRUCTION SHEET

The enclosed 120 ml. bottle contains 15 ml. of 6N hydrochloric acid to protect epinephrine and its derivatives from oxidation.* Its contents should be emptied into a chemically clean gallon jug rinsed with dis-

* If spilled or lost, any laboratory grade 6N hydrochloric acid (1 part concentrated acid to 1 part distilled water) can be substituted.

tilled water which is then to be used for an accurate 24-hour urine collection.* The enclosed cellophane protector should be used beneath the stopper of the jug while collecting the specimen. If a gallon jug is not available, any similarly cleaned glass bottle may be used. Special precautions must be taken to prevent contamination of the speci-

SAMPLE REPORT FORM

Name______________________________Date of Collection________

Blood pressure during collection hours________________________
Total volume of urine collection______________________(cc) (oz)
Period over which urine was collected____________________hours*

Before returning please review and mark the following check list.

1	Acid added to each voided sample (If not added, a new specimen should be collected)	Yes	No
2.	Cellophane cover over bottle stopper or enclosed cap used	Yes	No
3.	Any urine spilled or lost in collection	Yes	No
4.	Data and name label attached to bottle to be mailed	Yes	No
5.	Envelope self-addressed and enclosed	Yes	No

Name and address to which report is to be sent

____
____
____

* From the time of the last specimen which was discarded to that of the last specimen included in the sample

men. Metallic caps may not be used, since some metals catalyze the decomposition of the catechol amines Rubber stoppers, corks, and bakelite caps having a papered inner side often introduce fluorescent contaminants. To prevent this, first cover the mouth of the bottle with a portion of the enclosed cellophane and stopper with a cork or a clean bakelite cap whose inner paper portion is removed. Each voided sample must be put into the collection bottle as soon as possible. When all the urine has been collected, mix thoroughly and measure accurately the total volume in cubic centimeters or ounces

* If the patient is observed during an attack, a 4-hour urine specimen collected and *timed accurately* during the attack and following may be substituted provided at least 100 cc. are voided.

From this volume fill the enclosed bottle, apply cap tightly, label with the name and date in pencil and mail first class to the address on the enclosed label. The enclosed stamped envelope should be made out for the purpose of securing the proper address to which to send you the report. Fill out and return the form shown on page 255, in the package. If this is not received, it is impossible to give you an accurate report.

CHEMICAL METHOD

PRINCIPLE

The urine is passed through an alumina column that adsorbs 90 to 100 per cent of the catechol amines. They are then eluted with acetic acid and oxidized to adrenochrome by the addition of potassium ferricyanide at pH 6.5. Ascorbic acid is then added to stop further oxidation and the adrenochrome is rearranged to the highly fluorescent adrenolutin by the simultaneous addition of NaOH. The mixture is read in the Farrand photofluorometer* and compared with a similar urine sample in which, by omitting the ascorbic acid, oxidation has been permitted to go to complete destruction of the catechol ring structure. The norepinephrine derivative possesses only one fourth of the fluorescent activity of epinephrine and the two are not separated by this simplified test procedure. The result is expressed as micrograms of epinephrine. This is essentially the method of Von Euler and Floding (1955). Seventy to 90 per cent of epinephrine and norepinephrine added to the urine can be recovered by this procedure. Because of the variability of sources of reagents and unknown urine contaminants, it is well to test for the recovery of epinephrine by adding a small amount (0.5 μg. per 30 ml.) to a paired sample of each urine tested.

ANALYTICAL DETAILS†

The lower part of the glass column for the adsorption of catechol amines on alumina consists of a 17-cm. length of glass tubing (7 mm. O.D.) to which the upper part is sealed. The

* Farrand Optical Company, Inc., Bronx Blvd and E. 238th Street, New York 70, N.Y. Less sensitive photofluorimeters may be adequate but we have had no experience with them

† I am indebted to Mr Raymond Warzynski, Biochemist, University of Michigan Hypertension Clinic, for details of this procedure.

upper part consists of a 15-cm length of glass tubing (22 mm. O.D.) to which a short side arm tube is sealed 2 cm. from the top.

Preparation of Alumina. 40 Gm. of Fisher's Adsorption Alumina* is placed in an Erlenmeyer flask and boiled gently with 200 ml. of approximately 2N HCl for 20 minutes. Swirl flask frequently to avoid bumping Filter on a Buchner funnel, using Whatman filter paper No 50, under vacuum (water-aspirator). Wash with 200 ml. of approximately 2N hot HCl. Transfer to a 250 ml. graduated cylinder, add 200 ml. of distilled water. (All distilled water in the method is passed through an ion-exchange resin to give the equivalent of triple-distilled water.) Insert glass stopper and shake until the alumina is in suspension. Allow the alumina to settle and decant the water. Repeat this operation 15 to 20 times. At this point the pH of the wash water will be about 3 5. It is very important in the first few washings to decant the water before all the finely divided alumina has a chance to settle If this is not done, the subsequent chromatograms run very slowly and may even stop completely. The alumina is then dried at 300° C. for 3 hours and stoppered in a tightly closed bottle.

Preparation of 0 2M Sodium Acetate Solution. 27.2 Gm. of reagent $NaO_2C_2H_3 \cdot 3H_2O$ are made up to 1 liter. Remove traces of heavy metals with amberlite resin IR 120 (Rohm and Haas). About 150 ml. of the resin is stirred with three successive portions of distilled water and the water decanted. Transfer to the Buchner funnel, wash with distilled water, and divide the resin in half. To one half add 1 liter of the acetate solution and shake gently for 10 minutes. Allow to stand overnight. Decant solution into another container, containing the other half of the resin Shake again for 10 minutes, filter, and adjust the pH of the solution to 8 4 with 0.5N sodium carbonate solution, using a glass electrode

Preparation of the Alumina Column In the bottom end insert a glass wool plug. Add 1 Gm. of alumina and tap the column

* Fisher Scientific Company, 635 Greenwich Street, New York 14, N.Y.

down gently. Add 5 ml. of the above sodium acetate solution and allow it to pass through. When the level of the solution drops to the top of the alumina, a small cellophane-covered rubber stopper may be inserted beneath to hold the column until the urine is added. Never allow the level of the liquid in the column to drop below the top of the alumina.

Adjustment of the pH of the Urine. If urine is cloudy, remove sediment by centrifugation. Place about 40 ml. in a small beaker and adjust the pH to 8.40 (8.35 to 8.45) by adding small amounts of solid sodium carbonate and stirring rapidly with a glass rod. When the pH reaches 5.5 to 6, add 0.7 Gm. sodium thiosulfate crystals to protect the epinephrine from oxidation. When the correct pH is reached, the urine should be put through the column as soon as possible. The pH is determined with a glass electrode. If a precipitate is deposited or the solution becomes very cloudy (in some urines phosphate is precipitated at this pH), remove by centrifuging the urine for 3 minutes.

Preparation of the Eluate. Thirty milliliters of the urine is placed in the chromatogram tube. The tube is stoppered with a cellophane-covered rubber stopper, and the side arm tube connected by a rubber tube to a nitrogen cylinder or other source of positive pressure having a valve that will permit the flow of the gas to be carefully controlled. After the urine is added, the bottom stopper is then removed and the urine is allowed to flow through at about 1½ ml. per minute by adjusting the pressure of the gas. This takes about 20 minutes. When the level of the urine reaches the top of the alumina, 5 ml. of the sodium acetate buffer is added (place pipette tip against the side of the tube and wash down sides of the tube). When this runs through under the pressure of gas, add 5 ml. of distilled water and run through under pressure. The filtrate is discarded, and a 15 ml. graduated centrifuge tube is placed under the chromatogram tube. Now pass through 5 ml. of 0.2N acetic acid, followed by 5 ml. of distilled water. The eluate is 10 ml. Add a drop or two of water if necessary to make up to volume. Stopper with a cellophane-covered rubber stopper and invert a few times.

OXIDATION OF EPINEPHRINE TO ADRENOCHROME AND CONVERSION TO ADRENOLUTIN.

Solutions.

1. Potassium Ferricyanide (0.25 per cent):
   0.2 Gm. dissolved in 80 ml. distilled water. Store in refrigerator. Make fresh every two weeks.
2. Sodium Hydroxide (20 per cent):
   20.6 Gm. of NaOH pellets (97 per cent NaOH) dissolved in 100 ml. distilled water.
3. Ascorbic Acid (2 per cent):
   0.2 Gm. of pure ascorbic acid dissolved in 10 ml. distilled water. Make fresh daily.
4. Sodium Ascorbate:
   0 5 ml. of ascorbic acid solution is added to 5 ml. of sodium hydroxide solution *immediately* before using.
5. 1M Acetic Acid Solution:
   57.5 ml. of glacial acetic acid made up to 1 liter with distilled water.
6. 1M Sodium Acetate Solution:
   136.1 Gm. $NaO_2C_2H_3 \cdot 3H_2O$ made up to 1 liter with distilled water.
7. 1M Sodium Acetate Buffer (pH 6.50):
   To the sodium acetate solution add sufficient acetic acid solution until the pH is brought down to 6.5. Determine with a glass electrode.
8. Epinephrine Standard (Adrenalin, Parke, Davis and Company, Item No. 88).

One-milliliter ampoules of Adrenalin chloride 1:1000 aqueous contain 1 mg./ml. of epinephrine. It should be diluted immediately before use. One-fourth milliliter is withdrawn into a 0.25 ml. tuberculin syringe and diluted to 50 ml in a volumetric flask. One milliliter of this solution "A" is diluted to 100 ml. with distilled water for the epinephrine standard. One milliliter of solution "A" is diluted to 10 ml. with distilled water and 1 ml. of this mixture is added to 30 ml. of urine for the epinephrine recovery test. The epinephrine standard represents 0.05 μg./ml. The added epinephrine represents 0.017 μg./ml. of the original urine.

The reaction is carried out in Pyrex test tubes (18 mm. O.D.

× 75 mm.). They are first optically matched. For a urine and epinephrine standard four tubes are set up, two for the adrenolutin fluorescence and two for the corresponding blanks. A fifth, containing reagent isobutyl alcohol is used to check the constancy of the energy output of the ultraviolet lamp.

Sample Scheme·

Tube		*1*	*2*	*3*	*4*	*5*
Original sample		*Urine*	*Urine blank*	*Urine with 0.5 μg. epinephrine per 30 ml.*	*Epinephrine standard*	*Standard blank*
Distilled H_2O	ml.	2.75	2.85	2.75	1.75	1.85
0.1*N* *acetic acid*	ml.	0	0	0	0.25	0.25
Eluate from original sample	ml.	0.25	0.25	0.25	0	0
Epinephrine standard 0.05 μg./ml.	ml.	0	0	0	1.0	1.0
Buffer pH 6.5	ml.	2.0	2.0	2.0	2.0	2.0
Add to above	At Time					
0.1 ml. ferricyanide solution	0 min.	+	+	+	+	+
1.0 ml. sodium ascorbate	4 min.	+		+	+	...
0.9 ml. sodium hydroxide	4 min.		+		..	+

Read in photofluorometer within 5 minutes.

The tubes are swirled after the addition of the eluate or standard, and again after the addition of the buffer, and the ferricyanide. After the addition of the sodium ascorbate or sodium hydroxide, the tubes are covered with cellophane, taken up with the thumb and index finger, and inverted a few times. The oxidation with ferricyanide is carried out for 4 minutes

With some urine samples the fluorescence has a tendency to increase on standing and it is best to make the readings as soon as possible. If the urine has a considerable amount of noradrenalin, the blanks will give lower readings with time owing to the slower destruction of the noradrenolutin. Use the lowest blank reading.

INSTRUMENT USED. The instrument used is a Farrand photofluorometer. The primary filter is B2, a double filter, Corning 5113, half standard thickness, and 3389, with 3389 adjacent to the light. This combination passes the 436 *mu* line. The secondary filter is PC 2, Corning 3486 As a secondary filter, a Corning 3384 may be tried. This gives higher readings, but the blanks are also higher.

Sample Calculation:

1. Urine:

$$X = \frac{\mu g.\ \text{of standard} \times (\text{tube 1} - \text{tube 2})^*}{\text{Deflection of standard solution}} = \mu g./0.75\,\text{ml. urine}$$

Since only 0.25 ml. of the 10 ml. of eluate is used, the above figure represents the amount of epinephrine in 0.75 ml urine.

$$X = \frac{0.05 \times 16.75}{59.50} = 0.01408\ \mu g./0.75\ \text{ml. urine}$$

$$\frac{0.01408}{0.75} = 0.01877\ \mu g./\text{ml. urine}$$

$\mu g./\text{ml.} \times$ 24-hr. urine volume = total output

0.01877×2178 ml. = 40 9 $\mu g./24$ hrs.

2. Recovery:

Amount of epinephrine added to 30 ml urine is.

$$\frac{0.5\ \mu g.}{30\ \text{ml. of urine}} = 0.01667\ \mu g./\text{ml.}$$

Amount found:

$$\frac{0\ 05 \times 30.25}{59.50} = 0.02542\ \mu g\ /0.75\ \text{ml. urine}$$

Or:

0.03389 $\mu g./\text{ml.}$ urine with added epinephrine
−0.01877 $\mu g./\text{ml.}$ urine

0 01512 $\mu g./\text{ml.}$ added epinephrine

Per cent recovery:

$$\frac{0.01512}{0.01667} = 90.7\ \text{per cent}$$

* Difference in fluorescence of sample and of urine blank.

APPENDIX 3

Fifteen-Minute Phenolsulfonphthalein Excretion Test

TECHNIQUE

1. The patient preferably should not have voided immediately prior to the test.
2. He is given 1½ to 2 large glasses of water (400 to 500 ml.) to drink.
3. Thirty minutes later exactly 6 mg. of phenolsulfonphthalein is given intravenously (failure to inject all the dye into the vein is a common source of error).
4. Patient empties bladder precisely 15 minutes later. Entire volume is collected and sent to the laboratory.
5. Urine volume is measured in a liter graduate. One to two pellets of NaOH are added to alkalinize the sample that is diluted to 1 liter with water and mixed thoroughly; an aliquot is filtered into a colorimeter tube.
6. This sample is compared photometrically at 520 mμ light absorption with a control sample containing 6 mg. of the dye diluted in a volume 1000 ml. The standard sample can be stored for one to two months without deterioration.
7. Dye excretion is expressed as percentage of the reading for the standard. Urine volume is also reported.

INTERPRETATION

Normal kidneys should excrete 25 to 35 per cent of the dye in 15 minutes. Early in renal failure the amount excreted in 15

minutes is reduced while the amount eliminated over the more conventional 2-hour interval may remain normal.

Urine volume should exceed 100 ml. if the result is to be acceptable. Errors usually produce apparently low results and are the result either of a low rate of urine flow, an incomplete emptying of the bladder in cases of urinary obstruction, or failure to inject all the dye intravenously. Doubtful tests should be repeated. Duplicate examinations should check within 2 per cent.

The test measures tubular secretory function and runs parallel to Diodrast or para-aminohippurate clearance. However, other tests of renal function usually show similar directional change. In patients with beginning azotemia, the 15-minute phenolsulfonphthalein excretion is reduced to 10 per cent or less (one third of normal). Blood levels of nonprotein nitrogen or creatinine are more useful in following the day-to-day changes in renal function in patients with definite azotemia.

INDICATIONS

Rapid renal function testing in patients without azotemia; confirmation of reported borderline values for blood urea, nonprotein nitrogen and creatinine; detection of deterioration or improvement in renal function when obvious excretory insufficiency is absent.

The test is preferred to other procedures for estimating renal function chiefly because it is simple, reproducible, and can be *completed in 45 minutes, while other tests are less convenient* for the patient and are subject to greater chances for error both in sample collection and in chemical analysis.

CONTRAINDICATIONS

None. The test is, however, relatively unreliable when obstructive disease is present unless a catheterized urine sample is obtained.

APPENDIX 4

Working Outline for the Diagnostic and Prognostic Evaluation of the Individual Patient With Diastolic Hypertension

1. *Diagnosis.* Necessary to exclude secondary forms of hypertension

Observation	*Finding*	*Possible diagnosis*	*Patient status*
Urinalysis	Albuminuria	Glomerular nephritis	——
	Pyuria	Pyelonephritis	——
BP or pulse in lower extremity	Reduced	Coarctation	——
Histamine or Regitine test	Positive	Pheochromocytoma	——
Serum potassium	Reduced	Primary Aldosteronism	——
I.V. pyelogram and/or aortogram	Unilateral abnormality	Unilateral renal hypertension	——

2. *Prognosis:* Necessary for planning treatment and evaluating progress

Observation	*Favorable*	*Unfavorable*	*Patient status*
Age at onset	After 50	Before 40	———
Sex	Female	Male	———
Race	Colored	White	———
Family history of vascular disease	Present	Absent	———
Repeated casual or home BP readings	Labile	Recent increase or	———
		Established elevation	———
	Below 200/110 mm. Hg	Above 200/110 mm. Hg	———
Neurological history	Negative	Focal cerebral episodes	———
Funduscopic examination	Normal or arteriosclerosis	Focal vasoconstriction	———
		Hemorrhage	———
		Exudate	———
		Papilledema	———
Cardiac history	Negative	Angina	———
		Dyspnea, etc	———
Cardiac examination	Normal	Increased apical thrust	———
		Gallop rhythm	———
Electrocardiogram	Normal or minor T wave changes	Left ventricular hypertrophy or progressive change	———
	No progression under observation	Left bundle branch block	———
		Coronary changes	———
Cardiac size by x-ray, fluoroscopy	Normal	Hypertrophy of left ventricle	———
		Cardiac dilation	———
Urinalysis	Normal	Albuminuria	———
15-minute PSP excretion	20–35%	5–20%	———
	No change on repeated determinations	Progressive impairment	
Nonprotein nitrogen	Normal	Elevated	———

APPENDIX 5

Techniques for the Treatment of Hypertensive Emergencies

1. INTRAVENOUS USE OF TRIMETHAPHAN (ARFONAD) (SARNOFF, 1952)

TECHNIQUE. Arfonad is supplied in 10 ml. ampoules containing 50 mg./ml. The contents of 4 ampoules (2.0 Gm.) are diluted in 500 ml. of 5 per cent glucose, and the bottle, intravenous tubing, and needle are flushed with this solution, which contains 4 mg./ml. This precaution permits a uniform concentration of the drug from the beginning of the infusion. Great care should be taken to see that the infusion is not started too rapidly, and the drug should be administered at a rate of 4 mg. per minute. Blood pressure should be recorded every minute. If the desired level is not reached within 2 to 3 minutes, the rate of infusion may be increased by 2 mg. per minute increments until the desired response is obtained. Continuous supervision of the infusion rate is necessary to maintain the desired level of blood pressure, which will increase to the pretreatment level within 10 to 30 minutes after stopping the infusion.

OBJECTIVE. The objective is to achieve and maintain either moderate blood pressure reduction (p. 185) or marked hypotension (p. 153). In the latter instance, the complication of oliguria and overhydration must be considered. No more than 1200 to 1500 ml. of solution should be given daily, and urine flow must be watched carefully when hypotensive levels are reached. It is usually wise to place an indwelling catheter in the bladder.

SIDE EFFECTS. Drowsiness and yawning occasionally occur during the infusion. Cycloplegia, dryness of the mouth, and reduction in bowel and bladder activity occur after several hours of treatment. Orthostatic hypotension is prominent and patients should not be allowed out of bed for some time after the infusion is stopped.

INDICATIONS. (1) Any acute hypertensive crisis requiring rapid and continued blood pressure reduction; (2) trial of acute antihypertensive treatment where it is desired to permit rapid restoration of the original blood pressure, if the reduced level is not well tolerated; (3) conditions in which it is desired to maintain the blood pressure at subnormal levels, as in hypotensive anesthesia, or after subarachnoid or other hemorrhage.

CONTRAINDICATIONS. Ileus, gastrointestinal obstruction.

ANTIDOTE. (1) For excessive hypotension the patient should be placed in the Trendelenburg position, and norepinephrine, neosynephrine, or other pressor agent administered intravenously. The frequent administration of 1 ml. amounts of prostigmine (NNR) will assist in restoring bowel activity when this has been excessively depressed.

2. THE USE OF INTRAVENOUS SODIUM NITROPRUSSIDE (PAGE, 1955)

TECHNIQUE. 1 Gm. of sodium nitroprusside $Na_2[Fe(CN)_5(NO)] \cdot 2H_2O$ is diluted in 200 ml. of distilled water and filtered through a Seitz Filter into a sterile bottle from which a 1 to 100 dilution can be prepared for intravenous administration. This solution will then contain 50 μg./ml. Kept in the refrigerator and away from light, the solution has remained stable and nontoxic for as long as two months, in our experience.

An infusion containing 50 μg /ml. of 5 per cent glucose is prepared as described above, and administered at a rate of 0.5 to 1.0 ml. per minute with a gradual increase as necessary up to 300 μg. per minute. The infusion rate must be closely supervised according to the response of the blood pressure, which should

be taken every minute or so during the infusion. There will be a prompt rise when the procedure is discontinued.

OBJECTIVE. Rapid and controlled reduction in blood pressure.

SIDE EFFECTS. The side effects include tachycardia, nasal congestion and rarely nausea and vomiting.

INDICATIONS. These are the same as for trimethaphan (Arfonad). This drug may be superior to trimethaphan in the patient who has become refractory to ganglion-blocking agents. It possesses the further theoretical advantage of avoiding parasympathetic blockade. This may be particularly helpful in prolonged infusions. The author's experience with this technique is *limited and the original reference should be consulted for further* details.

CONTRAINDICATIONS. None is recognized. However, this drug is converted into thiocyanate ion and prolonged infusion leads to an elevation of blood levels of thiocyanate. For this reason it is doubtful that treatment should exceed more than one to two days if the effects of thiocyanate toxicity (nausea, vomiting, dermatitis, and mental confusion) are to be avoided.

ANTIDOTE. Excessive blood pressure reduction, which is rare, should be treated with the usual pressor agents given while the patient is in the head-down position.

3. USE OF VERATRUM COMPOUNDS INTRAVENOUSLY (MEILMAN, 1952)

TECHNIQUE. The solution of protoveratrine A and B is marketed as Veralba (Pitman-Moore) and is provided in 10-ml. vials containing 0.2 mg. of protoveratrine A and B per milliliter of solution. The minimum single intravenous dose necessary to produce an acute blood pressure reduction lasting 15 to 30 minutes is 0.1 mg. The effect occurs from 8 to 10 minutes after the injection, which may be repeated in one hour without detectable cumulative effect.

A continuous infusion is carried out as follows: 0.1 mg. (0.5 ml. Veralba solution) is administered intravenously in a single priming dose. This is followed by the infusion of a solution containing 0.5 ml. of Veralba per 100 ml. of infusion fluid (.001 mg/ml.), which is allowed to enter the vein at the precise rate of 1.0 ml. per minute for 10 minutes, during which time the effect of the priming dose on the blood pressure will appear. If a satisfactory reduction in blood pressure is not secured, the infusion should be increased to 2 ml. per minute for the succeeding 10 minutes. If the blood pressure is not reduced, the rate is then increased to 3 ml per minute for 10 minutes, and further increments of similar magnitude may be tried every 10 minutes until a moderate blood pressure reduction is secured. The infusion must be continually supervised and the blood pressure and heart rate recorded every minute.

Side Effects. Nausea and vomiting occur after variable intervals and it is usually necessary to reduce or discontinue the infusion at this time to provide relief. Bradycardia accompanies the hypotension and one must watch for evidence of arrhythmia or heart block. These can be promptly abolished by atropine sulphate, 1 0 mg. intravenously, with only partial loss of hypotensive effects. Paresthesias about the mouth, throat, and chest will sometimes suggest an atypical form of angina pectoris; this is a common but unimportant side effect, not related to any measurable disturbance in the coronary circulation.

Indications. The drug is particularly useful in the acute severe hypertensive crisis associated with toxemia of pregnancy, in patients who have become refractory to ganglion blockade, or have other conditions in which the use of ganglion-blocking agents is not advised.

Contraindications. These include heart block or administration during concomitant treatment with large doses of digitalis. While rhythm disturbances are more likely to occur in the previously digitalized patient, atropine will prevent serious reactions. Neosynephrine and norepinephrine may be used for acute hypotension.

OTHER INTRAVENOUS VERATRUM PREPARATIONS. These include cryptenamine (Unitensin-Irwin Neisler) and alkavervir (Veriloid-Riker). The actions of these compounds are similar to those of protoveratrine. For Unitensin an initial intravenous infusion rate of 0.05 mg. per minute is recommended; for Veriloid 0.04 mg. per minute is advised. In either case the infusion should be reduced or omitted as soon as a fall in blood pressure and pulse rate are observed.

4. USE OF GANGLION-BLOCKING AGENTS INTRAVENOUSLY (FREIS, 1952)

TECHNIQUE. Various ganglion-blocking agents may be given intravenously for reduction of blood pressure in emergencies. The use of hexamethonium is described as an example. Other drugs that may accomplish this purpose are given at the end of this section.

Hexamethonium bromide (Bistrium-Squibb) comes in ampoules containing 25 mg. of hexamethonium ion per ml. One milliliter of the drug is diluted in 24 ml. of glucose or salt solution in a large syringe so that each milliliter contains 1 mg. of hexamethonium. With the patient in the sitting position a venepuncture is performed, and the syringe containing the hexamethonium is then attached to the needle and 1 ml. is injected rapidly. The blood pressure is taken in the opposite arm in one minute. The drug is similarly administered at one-minute intervals for 5 minutes. If the blood pressure has not fallen, the remainder of the dose may be given in 2-ml. units, since it is not likely that the patient will exhibit excessive sensitivity. Usually a response will be secured from 25 mg. of hexamethonium and will last from 2 to 4 hours, but when the patient has previously been receiving ganglion-blocking agents, it may be necessary to give as much as 50 mg. before the desired effect on the blood pressure is secured.

OBJECTIVE. Usually it is the desire of the therapist to secure a moderate blood pressure reduction. The goal of reducing the blood pressure in the sitting position halfway from the initial systolic level to 150 mm. Hg is usually satisfactory for most hypertensive crises. Reduction in the diastolic pressure is consider-

ably less than in the systolic reading because the effect is largely the result of decrease in venous return and cardiac output. When the blood pressure has been lowered, the reduction can be maintained if the total necessary intravenous dose is given subcutaneously every 4 to 6 hours as necessary for blood pressure elevations above a certain level. Such a plan is preferable to routine administration every 4 hours, since it achieves desired blood pressure reduction with minimum doses of the drug. This in turn reduces the parasympathetic blocking effects that may otherwise cause ileus. Strong laxatives should be administered to prevent such a complication.

SIDE EFFECTS. The side effects include blurred vision, dry mouth, decrease in bladder and bowel motility, and other effects common to all ganglion-blocking drugs.

INDICATIONS. The treatment is recommended for most hypertensive emergencies in which acute and relatively long-lasting blood pressure reduction is desired.

CONTRAINDICATIONS Intestinal obstruction or prior disturbance of gastrointestinal or bladder function is a relative contraindication to treatment. In severe uremia with the nonprotein nitrogen level exceeding 100 mg. per cent, the treatment will probably be ineffective and may complicate the management of the disease Ganglion blockade may disturb homeostatic adjustments to hemorrhage and should be given cautiously in cases of severe bleeding. Patients with increased intracranial pressure and azotemia are apt to respond with excessive and prolonged reduction of blood pressure to less than average doses. The treatment for severe hypotension is to place the patient in a head-down position and immediately begin infusion of a pressor drug (norepinephrine, neosynephrine, ephedrine, or other vasopressor agent). For severe distention and paralytic ileus, 1 ml. of prostigmine (NNR) may be given intramuscularly every hour.

OTHER DRUGS. Pentolinium, chlorisondamine, or trimethidinium methosulphate may be used provided the dosages given above for hexamethonium are divided by a factor of five. These agents

APPENDIX 6

Rauwolfia in the Chronic Treatment of Hypertension (Wilkins, 1952)

OBJECTIVE. Moderate, sustained reduction of blood pressure in orthostatic and recumbent posture with a minimum of side effects.

CHOICE OF PATIENT. As the sole antihypertensive drug or in combination with chlorothiazide, rauwolfia is recommended for mild and extreme labile hypertension and for mild and moderately severe established hypertension.

It may be useful in arteriosclerotic hypertension, and as an adjuvant to other regimens. It is not effective in malignant hypertension and rarely in severe established hypertension with vascular complications. It is not advised for patients defined as having "labile blood pressure" (see p. 72), nor usually for its tranquilizing effect alone. It is relatively contraindicated in the treatment of patients with a history of depression, peptic ulceration, gallbladder disease, or in those individuals with severe diarrhea, edema, mental confusion, obesity, or heart block.

Treatment should not be maintained in any patient unless a definite effect on his blood pressure can be established. Methods for such evaluation are described below.

PROSPECT OF SUCCESS. Twenty-five to 50 per cent of properly selected patients will show a drop of 15 mm. Hg or more in the mean blood pressure according to most studies (Sheldon, 1957; Krogsgaard, 1957).

Choice of Drug. Reserpine is prescribed either as Serpasil (Ciba), Reserpoid (Upjohn), or Sandril with Pyronil (Lilly). Other formulations containing active rauwolfia alkaloids are acceptable but will not be listed here since the chemically pure form has greater reliability and other ingredients in rauwolfia mixtures do not appear to have added hypotensive activity or other advantages.

TECHNIQUE OF TREATMENT EMPLOYED AT THE UNIVERSITY OF MICHIGAN HYPERTENSION CLINIC

1. Give reserpine 0.25 mg. three times daily for two months.

2. Record blood pressure and pulse rate at 2-week intervals if possible.

3. If at the end of one month the pulse has not fallen at least 10 per cent and side effects are not prominent, increase dosage to 0 50 mg. three times daily for the second month. If side effects are severe during the trial period, reduction of the initial dosage may make the trial period tolerable.

4. At the end of two months, evaluate results. Compare several pretreatment blood pressure records with all readings after 6 weeks of continuous treatment. Compare corresponding pulse rate determinations.

a. If the average systolic and diastolic blood pressure is reduced by 15 mm. Hg or more, continue treatment but gradually reduce the daily dose toward a level of 0.25 mg. on alternate days. Establish a permanent follow-up program. Warn both the patient and a relative of the possibility of a mental depression or hypertensive relapse.

b. If the blood pressure is not reduced but the pulse rate has fallen 10 per cent, the patient probably is resistant to treatment and the drug should be permanently discontinued.

c. If neither the blood pressure nor the pulse rate is lowered, the therapeutic trial may be continued another month.

Side Effects. Even when therapeutic value has been demonstrated in the individual patient, the physician must make sure that the side effects are acceptable. The following symptoms are often not recognized by the patient as due to treatment:

apathy, depression, fatigue, loss of initiative, chronic nasal obstruction, gastrointestinal symptomatology, particularly in patients with a history of peptic ulcer, diarrhea, or gallbladder dysfunction, and progressive weight gain. In most instances, if these side effects are not abolished by a reduced daily dosage the drug should be discontinued, since it is usually prescribed for mild forms of hypertension that do not immediately threaten life. When the drug is used in combination with mecamylamine in the treatment of severe hypertensive disease, the physician likewise must assure himself that the added depressor effect of rauwolfia justifies the side effects produced. Sometimes a similar treatment result can be achieved by increasing mecamylamine dosage alone, and the added effects of rauwolfia (usually chronic fatigue) can be eliminated.

Depression and less commonly agitation are the major serious side effects. The patient and a relative should be warned that they may occur insidiously and as a late side effect at any time during treatment. If they occur, the drug must be withdrawn for at least two to three weeks before concluding that the reaction is not caused by rauwolfia.

USEFUL DETAILS. Sandril with Pyronil (Lilly) is preferred when nasal congestion is severe. Unpleasant side effects are acute in onset and offset; blood pressure reduction is a slow process. Hence, the daily dose of the drug may be given at one time if it is desired to avoid side effects during special periods in the day. A large proportion of the daily dose can be taken at bedtime and thus promote sleep. If nocturnal effects are unpleasant the major portion of the daily dose can be administered in the daytime.

PROOF OF THERAPEUTIC EFFECTIVENESS. Any regimen that is believed to be effective because it lowers blood pressure from a pre-existing "control" level is always difficult to evaluate under the usual conditions of a private practice. A better evaluation is often achieved by omitting treatment or substituting a "placebo" such as phenobarbital. In patients previously on reserpine, such a treatment withdrawal for a period of 4 to 6 weeks coupled with frequent blood pressure and pulse measurements will best dem-

onstrate to the patient and physician the effectiveness of rauwolfia therapy in an individual case. Such an observation period also permits the patient to recognize precisely the degree of disability which may be produced by the side effects of rauwolfia.

COMBINATION REGIMENS

The combination of reserpine and chlorothiazide deserves special consideration. A synergistic action is possible (Freis, 1957). These drugs may be usefully combined in the long-continued control of milder forms of hypertensive disease, since the combination of maintenance doses of reserpine (0.25 mg. daily) and chlorothiazide (0.5 Gm. twice daily) is usually so free of side effects as to be acceptable for sustained treatment of asymptomatic hypertension. However, the lack of toxic effects from chlorothiazide must be assured before the drug is prescribed indefinitely for milder cases of hypertension. Prolonged treatment with chlorothiazide has so far been reported to cause only minor toxic effects such as gastrointestinal disturbance and dermatitis over a 12-month trial period in a few patients, while rauwolfia compounds have been given safely in the United States for 4 to 5 years and in India they have been used safely for many years.

PARENTERAL RESERPINE

Reserpine, 2.5 to 5.0 mg. given intramuscularly or subcutaneously, will produce a reduction in blood pressure in 15 to 30 minutes usually reaching a maximum in 2 hours. The dose may be repeated in 2 to 4 hours but usually larger doses or injections more frequently than every 6 hours are not more effective in lowering blood pressure. Profound somnolence and bradycardia are common side effects; a red flush may develop when the drug is given intravenously but the hypotensive effect by this route is not much greater or more rapid in onset than when the reserpine is given intramuscularly. Extreme hypotension rarely occurs with these doses and it is not necessary to follow the blood pressure closely after injection of the drug.

APPENDIX 7

Use of Chlorothiazide and Ganglion Blockade in the Long-Term Treatment of Hypertension (Hoobler, 1957a)

TREATMENT OBJECTIVE. When these drugs are given for the treatment of hypertension, it is expected that in all patients except those with arteriosclerotic complications of the disease the systolic blood pressure is to be ultimately reduced to 150 mm. Hg when taken in the standing position.

CHOICE OF DRUG. Chlorothiazide is the best available diuretic drug. Mecamylamine is the preferred ganglion-blocking agent. When it is necessary because of side effects to use another ganglion-blocker, trimethidinium or chlorisondamine is preferred; pentolinium may be used but is a less desirable choice. The initial and incremental doses of these drugs are respectively: 20 mg. three times daily (trimethidinium), 25 mg. twice daily (chlorisondamine) and 25 to 50 mg. three times daily (pentolinium).

CHOICE OF PATIENT. This treatment is indicated for malignant and severe established hypertension with or without complications. When azotemia, angina pectoris, cerebral thrombosis, or cerebrovascular insufficiency is present, the drugs must be used with great care if at all. Mild established hypertension or the labile forms of the disease are generally not treated. Symptomatic arteriosclerotic hypertension not responding to milder forms of

treatment may be managed with a conservative program using mecamylamine as described near the end of this section.

CONTRAINDICATIONS. In addition to those varieties of hypertension noted above, for which the treatment is not favored, mecamylamine should be used cautiously or not at all in cases of glaucoma, peptic ulcer, partial prostatic obstruction, diarrhea, and pulmonary conditions in which bronchial drainage must be maintained. The drug will not be helpful when severe postural hypotension with recumbent hypertension is already present, as may occur after lumbodorsal sympathectomy or adrenalectomy with partial steroid replacement. *Note.* Chlorothiazide should never be given to patients who have had adrenalectomy. Also, the treatment is not useful in hypertension associated with diseases for which the recumbent posture must be maintained. Severe prostatic or bowel obstruction, ileitis or ulcerative colitis, and bronchiectasis are absolute contraindications.

TECHNIQUE OF ADMINISTRATION

1. The patient* or a relative is instructed in the use of the sphygmomanometer and is taught to record on an appropriate form the blood pressure after one minute of quiet standing in the morning and evening of each day (usually before breakfast and dinner) so that a "control" period of blood pressure recordings from 7 to 14 days is established before treatment is commenced.

2. Chlorothiazide 1.0 Gm. twice daily is prescribed for 3 days to assure maximum fluid depletion and to increase sensitivity to subsequent blockade. The dose is then reduced to 0.5 Gm. before breakfast and at bedtime daily and maintained at this level indefinitely.

3. A mild laxative (milk of magnesia 30 ml. daily, cascara sagrada 0.32 to 0.65 Gm. daily) is prescribed to be taken every day beginning with the first day of mecamylamine therapy. The patient is also advised to incorporate fruit and vegetable laxa-

* With the Propper "Autosfig" the blood pressure can be taken by the patient himself and recorded on appropriate graphic forms provided by the company (see Fig. 1, facing p. 216).

tives into his diet. Otherwise he may take his usual foods, but salt is not to be added in the cooking or at the table.

4. After the above preparation, 2.5 mg. of mecamylamine is prescribed twice daily to be taken after each blood pressure reading.

5. Every three days the dose of mecamylamine is increased by 2.5 mg. morning and night until 10 mg. twice daily is being taken or a consistent blood pressure reduction to the predetermined goal has been reached. The laxative dosage may have to be increased to keep up with increasing parasympathetic blockade. For this purpose the author prescribes one tablet of Alophen (Parke, Davis) daily if the previous laxatives have not been effective. To avoid the risk of ileus the patient is told to interrupt treatment temporarily if more than two days pass without a bowel movement or if gross abdominal distention occurs.

6. The above program requires about two weeks for completion. At this time the patient is asked to return with his blood pressure records for evaluation of the therapeutic result. If the blood pressure has not fallen to the level planned, a further dosage increment is best managed by adding a progressively increasing noon dose of mecamylamine beginning with 2.5 mg. and increasing by the same amount every third day until the desired effect is secured. If the blood pressure records show considerable variability in the readings, individual doses may be readjusted for smoother control. Occasional dizziness at the noon hour suggests that too much drug is being taken in the morning dose. A reduction in the amount taken in the evening is advised if severe orthostatic hypotension persists for more than 15 to 30 minutes on getting up in the morning. In this manner, final adjustments are suggested to the patient who will learn by trial and error the best way to control the blood pressure. Often the initial objective is deliberately set at higher than the finally desired goal. Thus an initial reduction to 170 mm. Hg for the usual standing blood pressure may be taken as the first goal When the patient becomes used to the effects of blood pressure reduction and the manipulation of his dosage, progressively lower levels may be attained, including the final treatment objective of the lowest possible standing blood pressure that can be obtained without producing postural syncope.

7. Once control is well established, blood pressure determinations may be performed less frequently, but patients are urged to record their blood pressure at least several times weekly for the purpose of review and discussion at office visits, which may then be planned at bimonthly intervals or longer. Annually the patient should undergo careful examination to detect the appearance of certain vascular lesions (p. 265). This checkup assures that the vascular disease does not progress and indirectly confirms the adequacy of control of the blood pressure. At these annual examinations, papilledema should have improved or disappeared; no new retinal hemorrhages or exudates should be evident; albuminuria should have decreased or disappeared; renal function as tested by the nonprotein nitrogen level or the 15-minute PSP excretion test should have remained stationary or improved. Symptoms of cardiac insufficiency and of cerebral vasospastic episodes should no longer occur, and electrocardiographic abnormalities may gradually improve Focal retinal arterial vasoconstriction is the last vascular lesion to show improvement.

Side Effects. Dry mouth and some blurring of vision may occur. Little can be done to alter these effects although trimethidinium may be helpful as an alternate ganglion-blocking drug. Impotence is common; temporary and cautious omission of mecamylamine may be necessary to avoid this effect. Impotence may also be produced by chlorothiazide treatment alone. Both drugs should *never* be abruptly discontinued because a dangerous hypertensive "rebound" may occur. Constipation, ileus, and urinary retention may occur as a result of ganglion blockade. These symptoms must be treated by cautiously stopping the ganglion-blocking agent and giving prostigmine (NNR) 1 ml. intramuscularly every hour for 4 to 6 doses.

Gait disturbances, tremor, excitation, and mental confusion may follow prolonged mecamylamine treatment, particularly in patients with azotemia. Conversion to trimethidinium or chlorisondamine is indicated in these circumstances. The neurologic effects of mecamylamine may require several weeks to disappear.

Weakness, muscle cramps, and disturbances of cardiac rhythm may indicate electrolyte deficiencies produced by chlorothiazide

tives into his diet. Otherwise he may take his usual foods, but salt is not to be added in the cooking or at the table.

4. After the above preparation, 2.5 mg. of mecamylamine is prescribed twice daily to be taken after each blood pressure reading.

5. Every three days the dose of mecamylamine is increased by 2.5 mg. morning and night until 10 mg. twice daily is being taken or a consistent blood pressure reduction to the predetermined goal has been reached. The laxative dosage may have to be increased to keep up with increasing parasympathetic blockade. For this purpose the author prescribes one tablet of Alophen (Parke, Davis) daily if the previous laxatives have not been effective. To avoid the risk of ileus the patient is told to interrupt treatment temporarily if more than two days pass without a bowel movement or if gross abdominal distention occurs.

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a program of intermittent administration of mecamylamine has occasionally been useful (pp. 57, 283). It has been used in arteriosclerotic hypertension to alleviate nocturnal symptoms such as dyspnea and early morning headaches. The smallest dose of mecamylamine that abolishes the symptom or modestly reduces the standing blood pressure in the morning is prescribed. When the drug is given in the evening the recumbent pressure may not be lowered but a redistribution of blood occurs in such a way as to relieve many nocturnal symptoms However, the patient should be warned that because of the influence of ganglion blockade, he is susceptible to sudden syncope on arising at night. The drug should be given early enough in the evening so that postural hypotension the following morning is not prominent. Chlorothiazide should first be administered since its action may obviate the need for mecamylamine.

3. Combinations of Other Drugs with Chlorothiazide and Mecamylamine The addition of reserpine to the regimen is made for any one of the following reasons: (1) excessive constipation, (2) increased nervousness or irritability, (3) wide fluctuation in blood pressure, (4) dissatisfaction with the degree of blood pressure reduction achieved, and (5) an unusually large orthostatic blood pressure gradient and a very high recumbent pressure. The method of addition of reserpine is the same as that followed when this drug is used alone in the treatment of hypertension (Appendix 6, p. 275). After the drug has been given a fair trial for several months it is important to determine whether the addition of this agent has improved blood pressure control enough to justify any additional side effects that may have been created. If such improvement cannot be demonstrated, it is advisable to discontinue the reserpine in such cases.

The addition of hydralazine to the mecamylamine regimen in our experience has only occasionally been of added benefit to the therapeutic program. With this drug, however, it is possible to reduce the amount of mecamylamine required to control the blood pressure, and sometimes to decrease the orthostatic blood pressure gradient. The combination of this drug with pentolinium has been found useful by Schroeder and Perry and the details of their treatment program are given in Appendix 11, p. 299.

in the presence of salt restricted diets. This may be confirmed by determining serum sodium and potassium levels when such symptoms occur. Treatment may also require potassium supplementation or cautious administration of sodium chloride.

PROSPECT OF SUCCESS. With the regimen as described, the morning and evening standing blood pressure should be maintained at or below systolic levels of 150 mm. Hg in nearly all hypertensive patients without causing excessive or intolerable side effects. The recumbent blood pressure, on the other hand, rarely falls to a similar extent Even when chlorothiazide is not used in the regimen, some 70 to 80 per cent of the patients may be successfully managed by mecamylamine alone (Cottier, 1957).

USEFUL DETAILS OF MANAGEMENT

1. INDUCTION OF TREATMENT IN THE HOSPITAL. The three-day intervals between dosage increments may be shortened to one day intervals provided good bowel control is maintained and the patient is hospitalized. Except for chlorothiazide, no other adjuvant drug is prescribed in the hospital, so that both patient and physician can distinguish the side effects and therapeutic value of each component as it is added to the regimen. Lying and standing blood pressure readings should be taken four times daily since the orthostatic gradient will measure the specific effect of ganglion blockade as opposed to the generally hypotensive effect of hospitalization. It is common to find these two influences so effective in reducing the blood pressure that one is often tempted to discharge the patient without careful instructions about the probability that on discharge dosage will have to be increased to suppress the hypertension. An early appointment for a return visit to the office or clinic should be arranged to evaluate the patient's success in regulating his blood pressure in the home.

2. MODIFIED TREATMENT PROGRAM FOR INTERMITTENT BLOCKADE. For patients with annoying hypertensive symptoms, for the very elderly, and for those who are unable to tolerate large doses of ganglion-blocking agents or to take their blood pressures at home,

a program of intermittent administration of mecamylamine has occasionally been useful (pp. 57, 283). It has been used in arteriosclerotic hypertension to alleviate nocturnal symptoms such as dyspnea and early morning headaches. The smallest dose of mecamylamine that abolishes the symptom or modestly reduces the standing blood pressure in the morning is prescribed. When the drug is given in the evening the recumbent pressure may not be lowered but a redistribution of blood occurs in such a way as to relieve many nocturnal symptoms. However, the patient should be warned that because of the influence of ganglion blockade, he is susceptible to sudden syncope on arising at night. The drug should be given early enough in the evening so that postural hypotension the following morning is not prominent. Chlorothiazide should first be administered since its action may obviate the need for mecamylamine.

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The side effects of hydralazine are reduced by prior treatment with ganglion-blocking agents but they may nevertheless prove troublesome. The section on hydralazine treatment alone (Appendix 9, p. 294) should be consulted in this regard.

4. Proof of the Effectiveness of Treatment. Although prolonged treatment withdrawal may carry some risk, the omission of an occasional dose of one or the other of these drugs for a day or two, accompanied by careful monitoring of the blood pressure, is an effective means of demonstrating to the patient and physician the continuing necessity for treatment. When other drugs are added to the chlorothiazide-mecamylamine treatment program, their occasional withdrawal is a good way to determine the value of the adjuvant drug. If mecamylamine dosage is maintained, such planned withdrawal of accessory drugs is an intelligent and safe method of evaluating their usefulness.

In patients receiving both chlorothiazide and mecamylamine, the former drug should not be omitted unless great care is used to raise the dose of [illegible] rebound is unusual. [illegible] is stopped. In rare [illegible] alone may be sufficient to control the blood pressure. It may be advisable, after the pressure is reduced, to attempt to withdraw mecamylamine from the combination to test the possibility that chlorothiazide alone will control the blood pressure. If mecamylamine withdrawal is planned, very close supervision of the blood pressure is necessary. Furthermore, it should be recalled that after prolonged treatment periods mecamylamine is excreted slowly and its effects may persist for several days. Consequently, the hypertensive rebound that follows withdrawal of this drug may be postponed as much as a week or so. Again, careful daily supervision of the blood pressure should prevent serious hypertensive recurrences.

5. Blood Pressure Records The standing blood pressure has a tendency to fall progressively with motionless standing. This often leads some patients to wait until the "lowest blood pressure" can be recorded. Since all these measurements are in a sense unphysiological and unrepresentative of the usual blood pressure in the seated or active state, it is well to insist on a

routine and standardized posture for taking the blood pressure. Since most patients achieve some stability after one minute of quiet standing it is advised that the blood pressure be recorded at this time regardless of any subsequent declines that may occur. If an excessive fall in blood pressure is not observed at the end of one minute of motionless standing, it is not likely that postural syncope will commonly occur.

6. CHLOROTHIAZIDE. It should be emphasized that at the present writing chlorothiazide appears reasonably nontoxic on prolonged use. Revision of these remarks and exclusion of this agent from the treatment program would be necessary if any serious or irreversible damage to even a few patients were reported after more prolonged usage. It should be remembered that control of the blood pressure would still be possible with mecamylamine alone *in at least 60 to 80 per cent of patients without the* use of chlorothiazide. Furthermore, the precise dosage and the effect of salt intake on the action of this diuretic have not been completely evaluated Excessive salt intake can certainly nullify the effect of chlorothiazide while a marked restriction of sodium in the diet to the 200 mg. level may render smaller doses of the diuretic effective. The present program has been devised around an average low salt diet and an average daily dose of chlorothiazide Since there is some risk of potassium depletion the drug should be prescribed in the morning and late evening so as to allow a brief period of "escape" from its effects during *the evening meal, on the assumption that potassium repletion* may occur at this time. This technique, which has been advised by Freis, has resulted in no difficulty with hypokalemia even when potassium supplements are not given. However it is wise, both for its laxative effects and to provide a good source of potassium, that daily fruit juice be taken by the patient, preferably with the evening meal. It is becoming increasingly apparent that the dosage of chlorothiazide recommended in this regimen is inadequate for a few patients who apparently need a greater degree of "desalting." It may therefore be advisable to use the larger doses of the drug (2 Gm. daily) for more than the first three days in some cases, as well as to prescribe a 0.5 Gm. tablet 4 times daily for temporary maintenance when blood pressure tends to rise unexpectedly. If this maximum dosage

regimen is maintained for more than several weeks, potassium supplements should be given and serum sodium and potassium levels followed closely. There is at present some evidence that intermittent periods of increased salt depletion may improve the blood pressure control and that omission of the extra dosage of chlorothiazide will thereafter result in no immediate loss of added hypotensive effect, particularly if dietary salt restriction is maintained.

7. CONTROL OF MECAMYLAMINE DOSAGE. The effects of various manipulations of dosage have been stressed in the section on technique of treatment. Other modifications may be described here. Sometimes the drug is best given four times daily when control appears erratic. The preference for the twice-a-day administration accords with the convenience of the patient, who may then take the medication in his home before breakfast and dinner. *It is advised* that the second dose be taken *early enough* that some orthostatic benefit may be achieved after dinner and the morning orthostatic hypotension be correspondingly reduced. In some instances it is preferred to delay the evening dose until bedtime if a good reduction in the early morning blood pressure is not achieved. When there is evidence of irregular control of the blood pressure, it is of course recommended that the readings in the home be made at other intervals than suggested in the simplest program outlined. It will usually be found that the standing blood pressure after lunch is somewhat lower than the usual readings recorded in the morning and before dinner and that the late evening blood pressures are somewhat higher than this average level. Usually, however, these differences are not great, owing to the prolonged action of mecamylamine.

Some confusion occurs when the dosage ordered in the hospital is made to depend on a predetermined blood pressure level. As with insulin for the management of diabetes, the less that random manipulation of doses is permitted, the more rapidly is good control achieved. Therefore, while it is advisable to establish a predetermined level at which the dose of the drug should be reduced or omitted, it is wise to have the nurse consult the physician before such an automatic change in dosage is carried out. Thus if a goal of a systolic blood pressure of 150 mm. Hg in the standing position is set, it may be advisable not

to change a single dose despite a further reduction to 130 mm. If the dose is decreased, it should be reduced by 2.5 mg. rather than omitted entirely. Frequently such low readings are only temporary and repetition after a few minutes will confirm the need for the usual dosage of the drug. If an excessive dose is given on any one occasion, protection from adverse hypotensive effects is usually complete if the patient lies down. Such instructions should be part of the training program for both the patient and the nurse who is to deal with this disease.

Mecamylamine is available in the 2.5- and 10-mg. tablet size and an error could easily be made by the patient or by the nurse giving the drug in the hospital. For this reason, it is preferred to keep only one size of tablet for mecamylamine available in the hospital and clinic so as to avoid any possibility of confusion.

8. CONTROL OF MECAMYLAMINE SIDE EFFECTS Ileus may occur in association with diarrhea when a fecal impaction is present. This is usually manifested by gross distention and absent bowel sounds; enemas combined with manual removal of the obstruction may prove necessary. Prostigmine (NNR), 1 ml. every hour subcutaneously is well tolerated and effective for ileus when fecal impaction is absent. If such drug treatment is not effective and the patient becomes seriously ill, it may be necessary to create a colostomy to remove retained intestinal secretions. Ileus that fails to respond to withdrawal of the drug and to prostigmine is of serious import and a surgeon should be called into consultation.

Prostatic obstruction may be precipitated by the weakening effect of ganglion blockade on the urinary bladder in patients with benign hypertrophy of the prostate. In the presence of a history of hesitancy of urination or other obstructive signs, ganglion-blocking agents should be prescribed with care.

9. FACTORS THAT ALTER SENSITIVITY TO GANGLION BLOCKADE. Vasodilating and dehydrating influences are frequently reasons for the onset of increased sensitivity to mecamylamine. Conditions that divert blood from the circulation such as alcohol ingestion, heavy meals, hot weather, or heavy muscular work may increase the blood pressure response to mecamylamine. This potentiation is also observed after the dehydration produced by

regimen is maintained for more than several weeks, potassium supplements should be given and serum sodium and potassium levels followed closely. There is at present some evidence that intermittent periods of increased salt depletion may improve the blood pressure control and that omission of the extra dosage of chlorothiazide will thereafter result in no immediate loss of added hypotensive effect, particularly if dietary salt restriction is maintained.

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APPENDIX 8

Use of Protoveratrine in the Long-Term Treatment of Hypertension (Hoobler, 1952)

OBJECTIVE. The objective of treatment is the maximum reduction of blood pressure that may be produced by oral medication without provoking too frequent nausea or vomiting. All veratrum compounds have a "threshold" below which no effect on blood pressure or pulse rate can be observed. At a dose level slightly above that required for depressor action an emetic response is produced. Intermittent dosage appears to achieve more depression of the blood pressure without nausea than may be achieved by fixed equal daily doses.

CHOICE OF DRUGS. Mixed alkaloids are similar in effects to purified preparations but their assay is less accurate. It is possible that some contain emetic alkaloids that do not contribute to the hypotension. For this reason, only purified preparations will be considered, although many veratrum mixtures are also effective and could be used in the manner described below for the protoveratrines.

Provell Malleate (Lilly) and Veralba (Pitman-Moore) are purified mixtures of equal parts of protoveratrine A and B. Protoveratrine B is not absorbed in usual oral dosage but is equidepressor when given intravenously (Winer, 1956). If protoveratrine A is made available at a later date, it may be substituted for the mixture of A and B in the oral dosage given below provided the recommended dose is reduced by one half.

hemorrhage, vomiting, diarrhea, and mercurial injections. Chlorothiazide administration may aggravate such hypotensive influences. Certain infections, even without fever, may reduce the blood pressure and increase the apparent response to ganglion blockade. Invasion of gram-negative organisms from the urinary tract is the commonest cause for unexplained severe hypotension in patients under treatment with ganglion-blocking agents. Virus infections such as the common cold and influenza may produce a similar effect on the blood pressure, particularly when ganglion blockade is present. The depressor effects may last for some weeks after overt signs of the viral disease have disappeared.

Loss of sensitivity to mecamylamine is a result of fluid retention from any one of a variety of causes, such as premenstrual edema, steroid administration, withdrawal of chlorothiazide, and impending cardiac failure.

10. Treatment of Severe Hypotensive Reactions. When there is an abrupt and marked change in sensitivity or an inadvertent overdose of ganglion-blocking agent (as, for example, when the dose of quaternary ammonium compound intended for oral administration is given subcutaneously by mistake) a medical emergency exists. The patient should immediately be placed in the head-down position and a vein entered by cut-down if necessary, to assure the prompt delivery of pressor agents into the circulation. If this is impossible, large parenteral doses of ephedrine, neosynephrine, or other available vasoconstrictors should be administered promptly into the deltoid muscle at such a point that a tourniquet can be applied proximally in the event the dose has been overestimated and intense hypertension ensues. If the vein can be entered, a carefully controlled and small dose of norepinephrine, neosynephrine, or other vasoconstrictor should be given by slow continuous infusion.* Restoration of function and consciousness occurs rapidly when pressor agents are promptly administered for circulatory collapse. Delay in treatment, however, may be fatal since prolonged cerebral anoxia is irreversible.

* [illegible] 2 ml of a 1:1000 "dilute to 20 ml. [illegible] in case of shock

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Choice of Patient. Since this regimen may intermittently produce nausea, it is indicated only for the treatment of severe and moderately severe cases of established hypertension with or without complications. It may be considered in cases where ganglion-blocking agents cannot be used, as in individuals who have severe constipation or would be likely to develop obstruction of bladder or bowel if given ganglion-blocking agents. Veratrum may be given in the usual dosage in azotemia, since the effects are independent of renal excretory function. Toxemia of pregnancy is frequently treated with veratrum since this drug appears to have no adverse effect on the fetus.

Contraindications. The effects on cardiac rhythm largely result from marked vagal stimulation. In patients with heart block of varying degrees, the drug should not be given, nor is it advised during the process of rapid digitalization. In the presence of angina pectoris, coronary thrombosis, cerebral thrombotic syndromes, or other conditions that may be worsened by excessive hypotension or by nausea and vomiting, veratrum compounds should be prescribed with care.

TECHNIQUE OF ADMINISTRATION OF PROTOVERATRINE A AND B

1. After breakfast give 1.0 mg. of protoveratrine orally, followed in two hours by an added dose of 0.25 mg. Maximum bradycardia and blood pressure depression should occur 2 hours later and persist 3 to 4 hours. If no blood pressure reduction occurs:

2. Give 1.25 mg. the following morning followed in two hours by the "booster" dose of 0.25 mg. If no response:

3. Give 1.50, 1.75, or 2.0 mg. as initial "loading" doses on subsequent days together with the same added dose of 0.25 mg 2 hours later.

4. When the threshold has been surpassed, the same dose day after day will achieve a remarkably similar effect.

5. The drug may be given in a similar manner in the evening for nocturnal dyspnea and other similar hypertensive complaints, but for unknown reasons the blood pressure reduction in the

evening is less marked. If such large doses are given twice daily, some tolerance and a considerable increase in emetic effect appear.

6. From preliminary reports it would appear that chlorothiazide will potentiate the depressor action of veratrum. It is not known whether the threshold for hypotensive action is lowered and a better hypotensive-to-emetic ratio is thereby achieved.

7. The majority of physicians use equal doses of veratrum three to four times daily. Reasons have been given above for the author's preference for large single doses. However, the alternate regimens may deserve trial and the following one is suggested:

Begin with 0.50 mg. of protoveratrine administered three times daily after meals and increase one dose by 0.1 to 0.25 mg. daily beginning with the morning dose, then the evening, and finally the noon dose. When the depressor threshold has been surpassed, the amount of the drug, time intervals of administration, and relation to meals should be kept constant. Usually a larger morning "loading" dose is prescribed but some investigators give the drug also at bedtime to reduce the need for a larger amount in the morning. This form of administration is successful in achieving a smooth but modest blood pressure reduction without nausea. Tolerance is said not to develop. It has the advantage of not provoking such a rapid fall in blood pressure as the plan outlined above, but in our experience is inferior because the reductions in pressure produced over long periods of time are unimpressive if episodes of nausea are kept to a minimum.

Side Effects A peculiar substernal and pharyngeal burning sensation occurs about one-half hour after the drug is ingested. The magnitude of this sensation bears a close relationship to the subsequent hypotension. It may serve to warn the patient of too rapid absorption and prepare him for later hypotensive and emetic effects.

A fall in blood pressure precedes the occurrence of nausea. Excessive hypotension is usually accompanied by weakness and inability to concentrate. Recumbent and standing blood pressures fall equally but the buffer reflexes remain intact. When severe hypotension is produced it can be offset by pressor agents such as ephedrine and neosynephrine, while atropine, which is

usually necessary to relieve coexistent nausea, will also raise the blood pressure somewhat by abolishing the bradycardia.

The pulse may drop to 40 to 50 beats per minute. Evidences of vagal stimulation may include varying degrees of heart block with ventricular escape. These are recognized by slight irregularities of the pulse and should promptly be relieved by 1 mg. of atropine sulphate intravenously. Probably many transient rhythm disturbances go undetected, but they must be benign, since sudden death or serious cardiac irregularities are not precipitated by veratrum treatment even in excessive dosage.

Emetic effects are the chief drawback to use of the drug in the long-term treatment of hypertension. These are usually heralded by salivation, anorexia, nausea, and finally vomiting. Food ingestion, or stimulation of visual or labyrinthine reflexes, will rapidly excite an emetic reflex in an individual sensitized by veratrum administration. For this reason, the drug is usually given after the meal. Atropine may provide some relief from nauseating effects but usually, as in motion sickness, the act of vomiting itself makes the patient feel better.

PROSPECT OF SUCCESS. This depends on the criteria for blood pressure reduction and the degree of side effects which the patient is willing to accept. In 60 to 80 per cent of patients, mean blood pressure reductions exceeding 20 mm. Hg in the diastolic range may be achieved for some part of each day by the regimen outlined above (Hoobler, 1952).

USEFUL DETAILS. 1. Oliguria appears during the depressor action of the drug. However, despite temporary reduction in renal blood flow patients with azotemia do not show a progression of their renal failure.

2. The main problem in treatment appears to be the production of a tissue concentration that lies between the emetic and depressor thresholds. This difference becomes less and less as treatment proceeds, and calls for very careful dosage control. Some therapists use 0.1 mg. increments or decrements in the final adjustment of the thrice daily doses.

3. The delay in response precludes careful control of dosage by blood pressure measurement. There is a 2- to 3-hour time lag

between ingestion of the drug and maximal depressor effects. Attempts to achieve precise dosage are complicated by daily variations in the rate of absorption.

4. Administration of the drug by the subcutaneous route may be tried in control of the blood pressure for short periods, as in toxemia of pregnancy. A starting dose of 0.25 mg. is recommended with repetition every 6 hours. Until the blood pressure is reduced, an increase of 0.05 mg. per dose can be used until a hypotensive effect is secured.

5. The magnitude and duration of residual effects presents another difficulty in the use of this drug. For several hours after the effects on the blood pressure have disappeared, a smaller amount of the drug is necessary to reach again the hypotensive threshold. Delayed release into the circulation from subcutaneous and intramuscular depots or gastrointestinal contents may explain the variations in the extent of nausea or hypotension after similar successive doses. When the drug is given by mouth, at least 12 hours must elapse before the same dose may be repeated with a reproducible effect; by injection, a period of 6 hours may be required.

COMBINATIONS WITH OTHER DRUGS In any combined program the dose of veratrum is critical. There is no convincing pharmacologic evidence for synergism between veratrum and other antihypertensive drugs. The best test of its added effectiveness is to follow the blood pressure closely during withdrawal of veratrum from a combination regimen. In the experience of some clinics, this test has confirmed the usefulness of veratrum in a combination program.

APPENDIX 9

The Use of Hydralazine in the Long-Term Treatment of Hypertension*

The early side effects of hydralazine are disturbing to many patients. These effects and the possible later development of the rheumatic and febrile syndrome that resembles lupus erythematosus have been deterrents to the use of this drug. Nevertheless, since hydralazine is a very potent antipressor agent, it should be used where indicated, and the early side effects and their control should be understood and anticipated (Taylor, 1952). The maintenance dose should be carefully adjusted and the patient should be apprised of the symptoms that characterize the rheumatic and febrile syndrome (Dustan, 1954).

TECHNIQUE OF ADMINISTRATION

Treatment may be instituted either in the hospital or in the office. As a general rule, it is accomplished more rapidly in the hospital, where the patient is under closer observation and the early side effects can be relieved more rapidly. The speed with which the physician is able to establish an adequate therapeutic dosage depends on the occurrence and control of side effects.

Hydralazine is given 4 times daily, after meals and at bedtime. The initial dose, which rarely causes side effects, is 25 mg. 4 times daily. Thereafter, the dose is increased at appropriate intervals by adding 25 mg. to each of the 4 daily doses (incre-

* The author is indebted to Dr. Harriet P. Dustan, Cleveland Clinic, Cleveland, Ohio, for contributing this section.

ments of 100 mg. per day) until a maximum level of 800 mg. per day has been reached or until a significant fall in blood pressure has occurred In the hospital, dosage increments can frequently be added every day; in office practice, it is wise to allow the patient a week to become adjusted to a given dose before changing to a higher level. If the patient develops side effects, the dose is not increased according to the schedules outlined below but is maintained (or even decreased by 100 mg. per day) until the side effects have subsided or have been controlled by appropriate measures.

For the hospital patient, the following schedule can be used: first day, 100 mg.; second day, 200 mg., third day, 300 mg; fourth day, 400 mg.; fifth day, 500 mg; sixth day, 600 mg.; seventh day, 700 mg; eighth day and thereafter, 800 mg This schedule should be changed if side effects develop.

For the office patient, the following schedule may be used: first week, 100 mg. per day, second week, 200 mg. per day; third week, 300 mg. per day; fourth week, 400 mg. per day; fifth week, 500 mg. per day; sixth week, 600 mg. per day; seventh week, 700 mg. per day, eighth week and thereafter, 800 mg. per day. This schedule should be changed if side effects develop.

Because the rheumatic and febrile syndrome seems more apt to occur when large amounts of hydralazine are given for long periods, the daily dose of 800 mg. is continued for only 2 to 3 months At the end of this time monthly decrements of 200 mg. per day are made until a maintenance dose of 200 mg. per day is reached. Thus a patient who has received 800 mg per day for 3 consecutive months will be instructed to take 600 mg. per day during the fourth month, 400 mg. per day during the fifth, and 200 mg per day during the sixth and succeeding months.

Side Effects. The side effects of hydralazine can be classified as early or late, according to their time of occurrence during treatment. The early side effects are for the most part attributable to acute circulatory changes, some of which may be due to histamine release and inhibition of histaminase. Thus, conjunctival suffusion and periorbital or dependent edema may be due to vasodilation; palpitation, tachycardia, and angina are due to increased cardiac output; headache is attributable to cerebral

vasodilation. Anorexia, which is common, and nausea and vomiting, which are occasionally seen, are not explained, nor is an "influenza-like" syndrome of generalized myalgia and fever. The tachycardia and associated palpitation may be bothersome and can best be mitigated by sedation with barbiturate and/or antihistaminic agents. If angina occurs, the dose of hydralazine should be promptly reduced and coronary dilators given in addition to sedative drugs. The headache usually responds to adequate amounts of antihistaminic agents and salicylate medication. The latter drug also relieves the "influenza-like" syndrome. Attention has been drawn by some to activation of peptic ulcers in susceptible patients; while this is uncommon the possibility should be borne in mind.

The late side effects in some instances resemble early rheumatoid arthritis and in others systemic lupus erythematosus (Schroeder, 1953). Should this late-appearing condition be allowed to persist, the patient may succumb to hyperpyrexia or pneumonitis. Since the severe form occurs only in patients who continue to take the drug while suffering from joint symptoms, it is important to discontinue hydralazine promptly on the appearance of the rheumatic state. As a rule the symptoms will respond within a day or two to such withdrawal. In those patients with severe systemic symptoms it is occasionally necessary, in addition, to administer adrenal cortical steroids or corticotropin.

COMBINATION PROGRAM. Chlorothiazide may be prescribed as an adjuvant in a dosage of 0.5 Gm. two to three times daily. For the combination of hydralazine with ganglion-blocking agents and other antihypertensive drugs, see Appendix 11, p. 299, and Appendix 12, p. 309. The pharmacologic actions of hydralazine are also discussed on p. 234.

APPENDIX 10

Use of Hydergine in the Long-Term Treatment of Hypertension (Kappert, 1949; Poldre, 1956)

OBJECTIVE. Average reduction in blood pressure of 20–25/15–30 mm. Hg.

CHOICE OF DRUGS. Hydergine (Sandoz) is available as an equal mixture of three dihydrogenated ergot alkaloids in tablets of 0.5 mg. each and in 1-ml. ampules containing 0.3 mg./ml. of the mixed alkaloids.

CHOICE OF PATIENT. Treatment is possible in all hypertensive subjects. In the elderly patient, one half the usual dosage is advised. In severe or malignant hypertension this program should be deferred since other more potent regimens are available.

TECHNIQUE OF ADMINISTRATION. 1. Give hydergine 0.3 mg. subcutaneously 2 to 3 times daily for 14 days.

2. Then give 0.5 mg. tablets 4 times daily together with 0.3 mg. subcutaneously twice weekly for 3 months.

3. If the blood pressure rises or symptoms recur, injections are given again as in (1).

CONTRAINDICATIONS. None recognized.

SIDE EFFECTS. Nasal obstruction, orthostatic hypotension, nausea, and vomiting are the commonest side effects, especially after parenteral administration.

PROSPECT OF SUCCESS. Little reduction in blood pressure can usually be accomplished over a long term, although relief of symptoms has been noted. Parenteral administration is more effective but is inconvenient. For a more complete discussion the reader is referred to p. 239.

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APPENDIX 11

Combined Use of Hydralazine and Ganglion Blockade* in the Long-Term Treatment of Hypertension

OBJECTIVES AND GENERAL PLAN OF THERAPY

In the malignant phase of hypertension, the ultimate objective of treatment is to convert the disease to its benign phase. In this latter condition, the objective is to lessen those changes which are related to elevated diastolic pressure. Specifically, therapy may be able to control heart failure, prevent progressive renal dysfunction, ameliorate such symptoms as headache or amblyopia, and perhaps lessen the increased rate of progression of atherosclerosis that accompanies hypertension.

The immediate objective of treatment is continuous control of the average diastolic pressure at normal or nearly normal levels. By the judicious use of a combination of oral ganglion-blocking agent and hydralazine, such control can frequently be maintained indefinitely. The general plan is to administer a blocking agent in gradually increasing doses until the average blood pressure approaches the desired level. Hydralazine is then added in the hope of obviating the wide fluctuations in blood pressure and the tolerance that characterize the use of blocking agents alone. Since the required amount of blocking agent often varies

* I am indebted to Drs. Harry Schroeder and H. Mitchell Perry, Jr., of the Hypertension Division, Washington University School of Medicine, St. Louis, Mo., for this contribution

considerably and in an unpredictable way, some method of relating each dose of drug to the level of blood pressure is advisable. In nonazotemic patients most of the absorbed blocking agent is excreted in the urine within a few hours; hence, frequent dosage is necessary to maintain a relatively constant concentration in the circulation. Although the action of hydralazine is more prolonged, a separate dosage schedule can be avoided by administering both drugs at the same time. To minimize the possibility of dangerous hypotension, changes in medication are made only once a day, and the dosages of the two drugs are not changed on the same day. Such treatment should be instituted in the hospital.

INCEPTION OF TREATMENT

The initial therapeutic step is to enlist the patient's complete co-operation. Therefore a minimum of an hour is spent in a frank and detailed discussion of his disease, including its prognosis when untreated. The exact plan of therapy, with its advantages and disadvantages, is explained both verbally and in a pamphlet. Each patient is specifically warned that he will probably feel worse before he feels better, but simultaneously the likelihood of ultimate improvement is stressed.

At present the best ganglion-blocking agents are pentolinium (Ansolysen), chlorisondamine (Ecolid), and mecamylamine (Inversine). Comparable oral starting doses are 20, 12.5, and 25 mg. respectively. Pentolinium and chlorisondamine are very similar to each other. Mecamylamine is somewhat different; it has the advantage of being almost completely absorbed from the gastrointestinal tract and the disadvantage of having produced neurologic manifestations in azotemic patients. Although the three can be used interchangeably, for the sake of simplicity only pentolinium will be considered below.

On the first day of therapy, specific orders for a relatively young patient without marked heart failure, encephalopathy, azotemia, or severe atherosclerosis might be:

"1. Take blood pressure in the sitting position every 4 hours.
2. Give 20 mg. of oral pentolinium every 4 hours day and night, if the systolic pressure exceeds 140 mm. Hg.

3. Give 30 ml. of milk of magnesia and 5 ml. of extract of cascara at night unless diarrhea is present.
4. Give 240 ml. of citrate of magnesia at noon if bowels have not moved during the preceding day."

Although it is the diastolic pressure in which one is interested, systolic pressure is used as a guide to dosage. The patients, who will eventually be taking their own blood pressure, can usually measure systolic pressure more accurately and reproducibly than diastolic pressure; obviously, changes in the two are closely related. Systolic pressure is measured with the patient in a sitting position. In that position a level of 140 mm. Hg, which most physicians consider the upper limit of normal, does not often cause young patients incapacitating hypotension when they stand. To obviate severe constipation it is necessary to prescribe daily laxatives at the same time as ganglion-blocking agents Patients are permitted to move about their rooms whenever they do not feel dizzy or faint after sitting on the side of the bed with feet dangling for a full minute.

On the second day the dose of ganglion-blocking agent is increased except in the rare instances when the mean systolic pressure has fallen to the desired level. Therapy is purposely begun with small doses in order to avoid hypotension in sensitive patients. The nursing orders are:

"1. Give 40 mg. of oral Ansolysen every 4 hours, day and night, if the systolic pressure in the sitting position exceeds 140 mm. Hg.
2. Give 20 mg. of oral Ansolysen every 4 hours, day and night, if the systolic pressure in the sitting position is between 125 and 140 mm. Hg."

On the third day it is usually necessary to increase the dose of ganglion-blocking agent again:

"1. Give 60 mg. of oral Ansolysen every 4 hours, day and night, if the systolic pressure in the sitting position exceeds 140 mm. Hg.
2. Give 30 mg. of oral Ansolysen every 4 hours, day and night, if the systolic pressure in the sitting position is between 125 and 140 mm. Hg"

Thereafter both the full and half doses of blocking agent are increased at daily intervals by similar increments (*20* and *10*

mg. of additional Ansolysen per dose respectively), until the systolic pressure begins to fall below 140 mm. Hg. The only criterion of adequate ganglion blockade is a normal or nearly normal blood pressure. We have found no untreated patient completely resistant to therapy, although the required dose of blocking agent is very variable. In one instance a maximum dose of 800 mg. of pentolinium every 4 hours was temporarily necessary to achieve a satisfactory response. Side effects are very troublesome, but patients can almost always be encouraged to tolerate them. Fortunately patients who are relatively resistant to the antihypertensive action of blocking agents are relatively resistant to side effects as well.

When the mean pressure approaches the desired level, hydralazine (Apresoline) is added to the regimen as follows:

"1. 25 mg. of oral Apresoline every 4 hours, day and night, regardless of blood pressure.
2 Give Ansolysen as before."

On the next day the dose of hydralazine is increased:

"1. Give 50 mg. of oral Apresoline every 4 hours, day and night, regardless of blood pressure.
2. Give Ansolysen as before"

The dose of hydralazine is increased at daily intervals by a similar increment (25 mg. of additional Apresoline per dose) until the intake of hydralazine approximates that of pentolinium. Roughly equal amounts of the two drugs seem to give the best results. If 100 mg. of pentolinium is the full dose that causes the systolic pressure to begin to fall below 140 mm. Hg, a first approximation of adequate control would be expected in nine days.

On the ninth day of therapy, typical orders for antihypertensive drugs might be:

"1. Give 100 mg. of oral Ansolysen every 4 hours, day and night, if the systolic pressure in the sitting position exceeds 140 mm. Hg.
2. Give 50 mg. of oral Ansolysen every 4 hours, day and night, if the systolic pressure in the sitting position is between 125 and 140 mm. Hg
3. Give 100 mg. of oral Apresoline every 4 hours, day and night, regardless of blood pressure."

At this point more exact regulation of blood pressure is often

indicated. If the mean level is too high, the dose of ganglion-blocking agent is increased; if the fluctuations are too great, the dose of hydralazine is increased. The regimen that has been outlined will almost always lower the systolic, and hence the diastolic, pressure to a satisfactory average level; however, the accompanying wide variations in pressure may produce symptoms. When such variations occur in a regular diurnal pattern, their cause can often be found and corrected. Even if no cause can be defined, predictable variations in pressure can usually be minimized by increasing the dose prior to a daily spike or by decreasing the dose prior to a daily trough in blood pressure. Bouts of hypertension may be correlated with psychic trauma and are frequently related to visits from relatives. There is a marked relationship between gastric contents and the efficacy of blocking agent. The most reproducible and at the same time the maximal absorption occurs when the drug is given on an empty stomach at least half an hour before meals.

MAINTENANCE OF THERAPY

After the blood pressure has been regulated at reasonable levels or at least in what seems to be the best possible manner in the hospital, full ambulation is permitted. Simultaneously one dose of medication is omitted during the night to permit 8 hours of unbroken sleep. Ordinarily no specific diet is required. Low sodium intake potentiates ganglion blockade, but it is rarely necessary and greatly inconveniences the patient. The diuretic, chlorothiazide, may produce the same result with less inconvenience. Other drugs such as digitalis, tranquilizers, or parasympathomimetics are seldom required. Before leaving the hospital each patient is given a sphygmomanometer and is taught to measure his own blood pressure accurately. Finally, detailed and individualized written instructions are prepared covering five major points.

1. The need for determining and recording the blood pressure on a regular schedule: Ordinarily five determinations a day permit optimum control of pressure. The first determination is made 15 minutes after arising in the morning, the last at bedtime, and the three other determinations are equally

spaced between these two. Slight variations may be necessary in order to have the ganglion-blocking agent taken on an empty stomach.

2. The dosage schedule for the ganglion-blocking agent: Ordinarily this drug is taken five times a day immediately after each blood pressure determination. The dose is the same as in the hospital, with full doses required when the systolic pressure is over 140 mm. Hg with the patient seated. Half doses are prescribed for systolic pressures between 140 and 125 mm. Hg.
3. The constant dose of hydralazine: This is to be taken five times a day. Ordinarily the dosage given in the hospital is continued.
4. The various situations that might require patients to consult the physician before the next scheduled visit: Specifically these are severe hypotension, recrudescent hypertension, urinary retention, uncontrollable constipation, and arthritis.
5. The return visit: Ordinarily patients are instructed to return one to four weeks after leaving the hospital, depending on their intelligence and co-operation as well as the anticipated difficulty in regulating their blood pressure at home.

Reregulation of the dosage of ganglion-blocking agent may be necessary, particularly on the first outpatient visit. The records of blood pressure and medication that the patient has carefully compiled at home serve as the basis for determining what changes are needed. An effort is made to manipulate the systolic pressure so that the average diastolic pressure of the seated patient is less than 100 mm. Hg. Experience suggests that individuals with this degree of control may eventually require gradually decreasing amounts of medication. The schedule for taking variable doses of blocking agent automatically adjusts intake to the level of systolic pressure. After some months of therapy it is often evident that adequate control of blood pressure requires decreasing amounts of blocking agent. At this time the physician should attempt to decrease the frequency and maximum size of the doses in a stepwise manner. If such changes are too precipitous, recrudescent hypertension indicates that the dose of blocking agent should immediately be increased. A relatively sudden improvement in control of blood pressure may herald

toxicity to hydralazine and demands an immediate decrease in the dosage of this drug. In an attempt to prevent such toxicity, hydralazine intake should be continuously lowered by the same percentage as the dose of blocking agent. As patients become increasingly able to maintain adequate control of their blood pressure on smaller and less frequent doses of drugs, they can be given at less frequent intervals. When normotension is approximated, little change in cardiac or renal function is anticipated and the danger of delayed toxicity to hydralazine has become minimal. Nevertheless, careful cardiovascular and renal evaluations should be performed at least once or twice a year, with particular attention to decreasing kidney function and genitourinary tract infection. Simultaneously one should watch for evidence of toxicity to hydralazine, with particular attention to arthritis, and for abnormal cephalin cholesterol flocculation or altered thymol turbidity.

SIDE EFFECTS

Marked and sustained elevation of the blood pressure can be lowered to normal or nearly normal levels by several techniques of varying efficacy, but significant lowering of the blood pressure is unpleasant, no matter what the method is. A lowered blood pressure by itself probably causes mental depression and loss of capacity for work. The additional side effects of ganglion blockade are episodic hypotension and parasympatholysis. Hydralazine may lessen the former directly and the latter indirectly by diminishing the requirement for ganglion-blocking agent. Patients who have no symptoms will seldom accept the side effects that accompany therapy. In contrast, patients with symptoms from their hypertensive cardiovascular disease may accept side effects in their stead, especially if they are told that these effects almost always improve in time.

Although side effects eventually diminish, at first it may be necessary to ameliorate them insofar as possible. Parasympatholytic effects are the only ones amenable to countermeasures. Constipation and urinary retention can be dangerous, whereas amblyopia, dry mouth, cold intolerance, nasal congestion, and impotence are only very annoying. With quaternary ammonium

blocking agents, such as pentolinium and chlorisondamine, constipation leads to an accumulation of the drug in the gastrointestinal tract. As a result there is an increase in the ordinarily small fraction of the drug that is absorbed. In addition to the laxative orders that have been cited, enemas and high fluid and fruit intake, particularly prune juice, are recommended. In rare instances, 2.5 to 10 or even 20 mg. of oral urecholine may temporarily be required with every dose of blocking agent. Persistent constipation is often improved with reserpine, which, however, usually causes some gain in weight and less frequently leads to severe depression or peptic ulceration. If urinary retention is uncorrected, it may produce infection and thereby further decrease renal function, unfortunately there is no adequate substitute for surgery when prostatic hypertrophy is present. Difficulty with visual accommodation often disappears within a matter of months; special glasses or pilocarpine eye drops may improve the situation. Dryness of the mouth may be helped by chewing gum or sucking hard candy; urecholine is often effective but is seldom warranted for this side effect alone. Susceptibility to cold is best corrected by warm clothing and warm environment. Antihistaminic agents may diminish nasal congestion. Impotence in the young male is the most persistent side effect and one that we have not succeeded in altering. Tachycardia and throbbing headaches that accompany the use of hydralazine alone are very rarely bothersome in the presence of blocking agent.

INDICATIONS AND CONTRAINDICATIONS FOR THERAPY

The prime indication for antihypertensive therapy is evidence that hypertension is doing harm. Either the accelerated form of the disease or a basal diastolic pressure of at least 110 mm. Hg, combined with decreasing renal function, cardiac failure, encephalopathy, or occasionally other related difficulties, constitutes presumptive evidence that hypertension is doing harm. Patients with such forms of the disease make up the minority who require therapy to prolong their lives. The majority of hypertensive patients present no clear-cut evidence that their elevated blood pressure is doing harm; many live with their disease and finally

succumb to complications of atherosclerosis. The certainty of undesirable side effects and the uncertainty of benefit following adequate ganglionic blockade usually make this treatment regimen an unrewarding procedure in asymptomatic hypertensive patients. Little risk has attended close observation of such patients provided treatment is instituted as soon as progression of the disease is evident.

In the presence of marked heart failure, encephalopathy, azotemia, or vascular insufficiency, the usual antihypertensive regimen must be modified. The first three situations require more rapid control and the last more cautious control of blood pressure than is routinely achieved. Acute left ventricular failure can be dramatically improved within minutes by administration of a parenteral ganglion-blocking agent. Except in extreme emergencies when the intravenous route is required, a satisfactory procedure is to inject 0.5 mg. of pentolinium into the deltoid muscle where a proximal tourniquet can be applied if necessary. Unless peripheral circulation is profoundly embarrassed, the maximum antihypertensive effect is evident in 15 minutes. Therefore successively doubled doses can be given at 15-minute intervals until the blood pressure falls. Hypertensive encephalopathy also responds dramatically to ganglion blockade. Encephalopathy renders a patient extremely sensitive to ganglion-blocking agents and thereby diminishes the safe initial intramuscular dose to 0.1 mg. of pentolinium. Mild or moderate azotemia, as in the terminal stage of malignant hypertension, constitutes an emergency since irreversible renal damage progresses rapidly as long as the blood pressure remains elevated. If the plasma contains less than 50 mg. of urea nitrogen per 100 ml. after correction of "prerenal" azotemia by hydration and digitalization, residual renal function is usually adequate to support life. Azotemia resulting from dehydration and cardiac failure is difficult to separate from that due to destruction of renal parenchyma. The prognosis is much better for prerenal than for renal azotemia. In the presence of any type of azotemia the dose of ganglion-blocking agent is gauged by the concentration of circulating urea rather than by the level of blood pressure. Ordinarily the diastolic pressure can be returned to normal or near normal levels but it may be necessary to do this in several stages. Nitrogen retention

may increase each time the blood pressure falls. Usually such increases are temporary. Angina pectoris or threatened stroke may complicate severe diastolic hypertension. Such situations are often improved by ganglion blockade; however, the blood pressure should be lowered cautiously and drugs must be stopped if symptoms become worse. Normal blood pressure greatly reduces the hazard of anticoagulant therapy.

In patients with severe heart failure and minimal diastolic hypertension, it is tempting to administer antihypertensive agents; however, therapy is usually valueless unless the diastolic pressure is 110 mm. Hg or more. Presumably the hypertension contributes so little to the over-all problem that its correction is of no avail. Similarly the patient with pure systolic hypertension is not improved by the currently available antihypertensive agents. It is not helpful to lower blood pressure from 200/90 mm. Hg to 140/30 mm. Absolute contraindications to ganglion blockade are few in very sick or moribund patients who have marked diastolic hypertension. The major one is uremia. When the level of urea nitrogen is more than 100 mg. per 100 ml. of plasma after prerenal azotemia has been corrected, antihypertensive therapy only hastens demise.

APPENDIX 12

Use of Chlorothiazide, Reserpine, Hydralazine, and Ganglion Blockade* in the Long-Term Treatment of Hypertension

THERAPEUTIC OBJECTIVE. Reduction of average diastolic sitting blood pressure *at home* to 100 mm. Hg or less.

DETAILS OF TREATMENT

1. Give chlorothiazide 0.5 Gm. 3 times daily for 3 days, then 0.5 Gm. before breakfast and at bedtime daily. Patient should avoid added salt at the table. If objective is not achieved in 7 days, add:

2. Reserpine 0.25 mg. 4 times daily for 2 weeks, then once daily at bedtime thereafter. If diastolic blood pressure exceeds 100 mm. Hg after third week, add:

3. Hydralazine 25 mg. 3 times daily (breakfast, 2 P.M., and bedtime). Raise by 10 mg. increments as tolerated to 50 mg, thrice daily. If the blood pressure still is not reduced add:

4. A ganglion-blocking agent (pentolinium 10 mg., chlorisondamine 12 mg, or mecamylamine 1.25 mg.) every 8 hours in gradually increasing doses until the therapeutic objective is attained.

5. When the desired blood pressure is reached, the dose of

* I am indebted to Dr Edward Freis, Chief of the Cardiovascular Research Laboratory, Georgetown University Medical School, for the details of this treatment program (Freis and Wilson, 1956b).

reserpine is omitted first, then the dose of the last drug to be added is reduced and finally omitted, provided the blood pressure remains below the goal set.

Side Effects. These are discussed elsewhere (pp. 274, 278). Precautions are the same as with other treatment programs. Chlorothiazide may produce reductions in blood potassium levels, and clinical evaluation of this agent has not yet been extensive enough to rule out the possibility of long-term toxic effects.

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